thalassemia reports

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14th International Conference on Thalassaemia and Other Haemoglobinopathies
16th TIF Conference for Patients and Parents

17-19 November 2017 • Grand Hotel Palace, Thessaloniki, Greece

For thalassemia patients with chronic transfusional iron overload...

Make a lasting impression with EXJADE film-coated tablets

The efficacy of deferasirox in a convenient once-daily film-coated tablet

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Reference: EXJADE® film-coated tablets [EU Summary of Product Characteristics]. Novartis; August 2017.

EXJADE®
(deferasirox) FILM-COATED TABLETS

Important note: Before prescribing, consult full prescribing information.

Presentation: Dispersible tablets containing 125 mg, 250 mg or 500 mg of deferasirox. Film-coated tablets containing 90 mg, 180 mg or 360 mg of deferasirox.

Indications: For the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta-thalassemia major aged 6 years and older. ♦ Also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: in pediatric patients with beta-thalassemia major with iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) aged 2 to 5 years; in adult and pediatric patients with other anemias aged 2 years and older; in adult and pediatric patients with beta-thalassemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older. ♦ For the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non–transfusion-dependent thalassemia syndromes aged 10 years and older.

Dosage: Transfusional iron overload

Dispersible tablets ♦ Recommended initial daily dose is 20 mg/kg body weight; consider 30 mg/kg for frequently transfused patients receiving >14 ml/kg/month of packed red blood cells (approximately >4 units/month) who require reduction of iron overload; consider 10 mg/kg for infrequently transfused patients receiving <7 ml/kg/month of packed red blood cells (approximately <2 units/month) who do not require reduction of body iron level; for patients already well-managed on treatment with deferoxamine, consider a starting dose of EXJADE that is numerically half that of the deferoxamine dose. ♦ EXJADE must be taken once daily on an empty stomach at least 30 minutes before food. ♦ Tablets to be dispersed in water or apple or orange juice (100-200ml). ♦ **Monthly monitoring of serum ferritin** to assess patient's response to therapy ♦ Dose to be adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 to 10 mg/kg. In patients not adequately controlled with doses of 30 mg/kg, doses of up to 40 mg/kg may be considered. ♦ **Maximum daily dose** is 40 mg/kg body weight. ♦ In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 micrograms/l), consider dose reductions in steps of 5 to 10 mg/kg to maintain serum ferritin levels within the target range. ♦ Interrupt treatment if serum ferritin falls consistently below 500 micrograms/l.

Film-coated tablets ♦ Recommended initial daily dose is 14 mg/kg body weight; consider 21 mg/kg for patients receiving >14 ml/kg/month of packed red blood cells (>4 units/month), and for whom the objective is reduction of iron overload; consider 7 mg/kg for patients receiving <7 ml/kg/month of packed red blood cells (<2 units/month), and for whom the objective is maintenance of the body iron level; for patients already well-managed on treatment with deferoxamine, consider a starting dose of EXJADE that is numerically one third that of the deferoxamine dose. For patients who are currently on chelation therapy with the dispersible tablet and switching to the film-coated tablet, the dose should be 30% lower, rounded to the nearest whole tablet. ♦ The film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, the tablets may be crushed and administered by sprinkling the full dose on soft food like yogurt or apple sauce (apple puree). The dose should be immediately and completely consumed, and not stored for future use. EXJADE should be taken once a day, preferably at the same time each day, and may be taken on an empty stomach or with a light meal. ♦ **Monthly monitoring of serum ferritin** to assess patient's response to therapy. ♦ Dose to be adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 3.5 to 7 mg/kg. ♦ Maximum daily dose is 28 mg/kg body weight. ♦ In patients whose serum ferritin level has reached the target (usually between 500 and 1,000 micrograms/l), consider dose reductions in steps of 3.5 to 7 mg/kg to maintain serum ferritin levels within the target range. ♦ Interrupt treatment if serum ferritin falls consistently below 500 micrograms/l.

Dosage: Non–transfusion-dependent thalassemia syndromes and iron overload

Dispersible tablets ♦ Recommended initial daily dose is 10 mg/kg body weight. Therapy should only be initiated when there is evidence of iron overload: liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) or serum ferritin consistently >800 micrograms/l. In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation. ♦ **Monthly monitoring of serum ferritin** ♦ Dose adjustment should be considered every 3 to 6 months in steps of 5 to 10 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 micrograms/l, and not showing a downward trend, and the patient is tolerating the drug well. Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 micrograms/l), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended. ♦ **Maximum daily dose** is 20 mg/kg body weight. ♦ In **pediatric patients** the dosing should not exceed 10 mg/kg; closer monitoring of LIC and serum ferritin is essential to avoid overchelation; in addition to monthly serum ferritin assessments, LIC should be monitored every 3 months when serum ferritin is ≤800 micrograms/l.

Film-coated tablets ♦ Recommended initial daily dose is 7 mg/kg body weight. Therapy should only be initiated when there is evidence of iron overload: liver iron concentration (LIC) ≥5 mg Fe/g dry weight (dw) or serum ferritin consistently >800 micrograms/l. In patients with no LIC assessment, caution should be taken during chelation therapy to minimize the risk of over-chelation. For patients who are currently on chelation therapy with the dispersible tablet and switching to the film-coated tablet, the dose should be 30% lower, rounded to the nearest whole tablet. ♦ **Monthly monitoring of serum ferritin** ♦ Dose adjustment should be considered every 3 to 6 months in steps of 3.5 to 7 mg/kg if the patient's LIC is ≥7 mg Fe/g dw, or serum ferritin is consistently >2,000 micrograms/l, and not showing a downward trend, and the patient is tolerating the drug well. Once a satisfactory body iron level has been achieved (LIC <3 mg Fe/g dw or serum ferritin <300 micrograms/l), treatment should be stopped. There are no data available on the retreatment of patients who reaccumulate iron after having achieved a satisfactory body iron level and therefore retreatment cannot be recommended. ♦ **Maximum daily dose** is 14 mg/kg body weight. ♦ In **pediatric patients** the dosing should not exceed 7 mg/kg; closer monitoring of LIC and serum ferritin is essential to avoid overchelation; in addition to monthly serum ferritin assessments, LIC should be monitored every 3 months when serum ferritin is ≤800 micrograms/l.

Dosage: Special population ♦ In moderate hepatic impairment (Child-Pugh B) dose should not exceed 50% of the normal dose. Should not be used in severe hepatic impairment (Child-Pugh C).

Contraindications: Hypersensitivity to deferasirox or to any of the excipients. ♦ Combination with other iron chelator therapies. ♦ Estimated creatinine clearance <60 ml/min.

Warnings/Precautions: ♦ Renal Function: Assess serum creatinine in duplicate before initiating therapy; monitor serum creatinine, creatinine clearance and/or plasma cystatin C levels prior to therapy, weekly in the first month after initiation or modification of therapy (including switch of formulation), and monthly thereafter. Dose reduction or interruption may be required in some cases where rises in serum creatinine occur. Postmarketing cases of renal failure (some requiring dialysis) have been reported. There have been reports of renal tubulopathy **with cases of metabolic acidosis,** mainly in children and adolescents with beta-thalassemia. Tests for proteinuria should be performed monthly. Refer the patient to a renal specialist and consider further specialized investigations (such as renal biopsy) if serum creatinine remains significantly elevated and another marker of renal function is also persistently abnormal. **♦ Hepatic Function: Monitor serum transaminases, bilirubin and alkaline phosphatase before the initiation of treatment, every 2 weeks during the first month and monthly thereafter. Interrupt treatment if persistent and progressive unattributable increase in serum transaminase levels occur. Postmarketing cases of hepatic failure (sometimes fatal) have been reported. Not recommended in patients with severe hepatic impairment (Child-Pugh C).** ♦ Caution in elderly patients due to a higher frequency of adverse reactions. **Not recommended in patients with a short life expectancy (e.g. high-risk myelodysplastic syndromes) especially when co-morbidities could increase the risk of adverse events.** ♦ Gastrointestinal irritation may occur. Upper gastrointestinal ulceration and hemorrhage, including ulcers complicated with digestive perforation, have been reported in patients, including children and adolescents. There have been reports of fatal gastrointestinal hemorrhages, especially in elderly patients who had hematologic malignancies and/or low platelet counts. Caution in patients with platelet counts <50 • 10^9/l and in patients taking anticoagulants or other drugs with known ulcerogenic potential. Acute pancreatitis has been reported, particularly in children and adolescents. ♦ Interrupt treatment if severe skin rash develops. ♦ Consider reintroduction at a lower dose followed by dose escalation. ♦ Severe cutaneous adverse reactions (SCARs), e.g cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and DRESS (drug reaction with eosinophilia and systemic symptoms) have been reported. Patients should be advised of the signs and symptoms of SCARs and be closely monitored. If any SCAR is suspected EXJADE should be discontinued immediately and not reintroduced ♦ Discontinue if severe hypersensitivity reaction occurs. ♦ Annual ophthalmological/audiological testing. ♦ Annual monitoring for body weight, height and sexual development in pediatric patients. ♦ Interruption of treatment should be considered in patients who develop unexplained cytopenia. ♦ Cardiac function should be monitored in patients with severe iron overload during long-term EXJADE treatment. ♦ Should not be used during pregnancy unless clearly necessary. If used, additional or alternative non-hormonal contraception is recommended. ♦ Not recommended when breastfeeding. ♦ Product contains lactose.

Interactions: Must not be combined with other iron chelator therapies ♦ Should not be taken with aluminum-containing antacids. ♦ Caution when combined with drugs metabolized through CYP3A4 (e.g. cyclosporine, simvastatin, hormonal contraceptive agents, bepridil, ergotamine). ♦ Concomitant use with potent UGT inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir, cholesteramine) may result in a decrease in EXJADE efficacy. ♦ Careful monitoring of glucose levels should be performed when repaglinide (a CYP2C8 substrate) and EXJADE are used concomitantly. EXJADE may also increase levels of other CYP2C8 substrates like paclitaxel. ♦ Consider monitoring of theophylline concentration and possible theophylline dose reduction. Interaction with other CYP1A2 substrates may be possible. ♦ Caution when combined with drugs with ulcerogenic potential (e.g. NSAIDs, corticosteroids, oral bisphosphonates) or with anticoagulants.

Adverse reactions: *Very common:* Blood creatinine increased. ♦ *Common:* Headache, diarrhea, constipation, vomiting, nausea, abdominal pain, abdominal distension, dyspepsia, transaminases increased, rash, pruritus, proteinuria. ♦ *Uncommon:* anxiety, sleep disorder, dizziness, cataract, maculopathy, deafness, laryngeal pain, gastrointestinal hemorrhage, gastric ulcer, duodenal ulcer, gastritis, hepatitis, cholelithiasis, pigmentation disorder, renal tubular disorder (acquired Fanconi syndrome), glycosuria, pyrexia, edema, fatigue. ♦ *Rare:* Esophagitis, optic neuritis, DRESS (drug reaction with eosinophilia and systemic symptoms). ♦ *Not Known (cannot be estimated from data):* Stevens-Johnson syndrome, pancytopenia, thrombocytopenia, neutropenia, aggravated anemia, hypersensitivity reactions (including anaphylactic reactions and angioedema), metabolic acidosis, gastrointestinal perforation, acute pancreatitis, hepatic failure, hypersensitivity vasculitis, urticaria, erythema multiforme, alopecia, toxic epidermal necrolysis (TEN), acute renal failure, tubulointerstitial nephritis, nephrolithiasis, renal tubular necrosis. ♦ Refer to the SmPC for a full list of adverse reactions.

Legal Category: country specific

Packs: country specific information

This medical product is subject to additional monitoring.

This will allow quick identification of new safety information.

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Please see your local Novartis representative for Full Product Information

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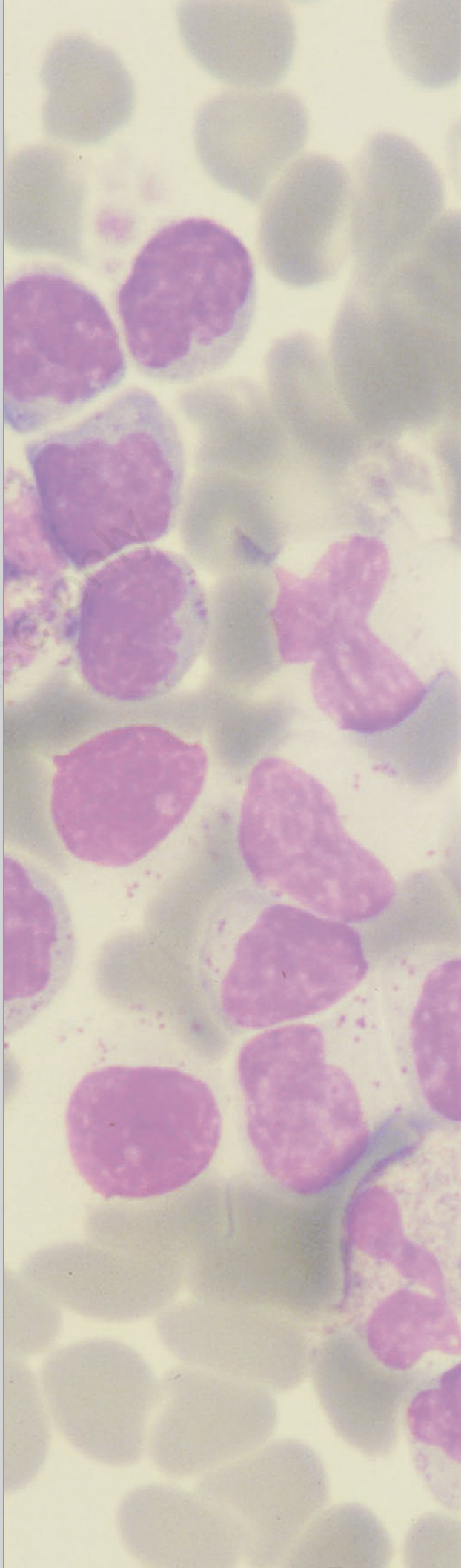

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14th International Conference on Thalassaemia and Other Haemoglobinopathies & 16th TIF Conference for Patients and Parents

17-19 November, 2017
Thessaloniki, Greece

Organized by the
Thalassaemia International Federation

In collaboration with
Greek Thalassaemia Federation

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City of Thessaloniki
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Proceedings Book

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Welcome messages

Dear Friends,

The 14th International Conference on Thalassaemia and Other Haemoglobinopathies & the 16th TIF Conference for Patients and Parents constitute the largest biennial educational event of Thalassaemia International Federation (TIF). Organized in collaboration with the Greek Thalasssaemia Federation (EOTHA), with the support of the Greek Thalassaemia Association (ESTHA) and the Hellenic Society of Haematology, the Conference took place on 17-19 November 2017, in the beautiful city of Thessaloniki in Greece. Moreover, the Conference has enjoyed the auspices of the Greek Ministry of Health, the Hellenic Center for Disease Control & Prevention and the City of Thessaloniki.

The Conference covered a broad range of topics, including all clinical aspects of current state-of-art diagnosis, treatment and monitoring of thalassaemia and other haemoglobinopathies,in addition to the recent scientific advances in the field and several additional topics concerning the holistic care of patients, such as the organization of multidisciplinary care, psychosocial issues and legal issues relevant to the accreditation and quality assurance of services. In several sessions, the presentations of medical experts or scientists were coupled with patients' perspectives and expectations presented by members of TIF's Expert Patients Panel.

Furthermore, topics on patient empowerment and capacity building, which are key features of TIF's work, were covered, with the Conference providing a unique forum of sharing knowledge and experiences and/or building new, and strengthening existing networks and collaborations.

As we all strive towards achieving the new set of goals set by the United Nations and World Health Organisation by 2030, promotion of patient involvement and ensuring patient-centredness in healthcare systems remain important, indispensable targets for TIF.

There is understandably still a long way to go considering the huge heterogeneity existing in the adoption of appropriate policies for the effective control of these disorders and the consequent gaps in equity of access of patients to quality healthcare and other care. However, science has and continues to meet patients' expectations for both health and quality of life – It is TIF's, and every other stakeholders', responsibility to work with the World Health Organisation, Regional decision-making bodies and national governments to ensure that these advances become available, accessible and officially adopted by all for the benefit of every patient wherever he/she may live.

This historic event will serve as a stepping stone to build a brighter future together for patients with haemoglobinopathies.

Cordially,

Panos Englezos
President,
Thalassaemia International Federation

Vassileios Dimos
President
Greek Thalassaemia Federation

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About the Thalassaemia International Federation (TIF)

The Thalassaemia International Federation (TIF) was founded by patients with thalassaemia and their parents in 1986 and registered in Cyprus as a Non-Profit, Non-Governmental Organisation, under the Cyprus Company Law in 1987. Governed by its constitution, the Federation is presided over by an 18-member Board of Directors (maximum two representatives per country), elected for a four-year term and comprised of no less than 50% of patients with thalassaemia.

MISSION

The development and implementation of national disease-specific programmes for thalassaemia in every country, which encompass both the component of prevention and that of management.

VISION

Establishment of equal access to quality health, social and other care for all patients with thalassaemia globally, in a truly patient-centred health care setting.

Noteworthy, TIF has been established to address, and by constitution to serve exclusively the needs of patients with thalassaemia globally through its activities. However, recognising the need and absence of strong patient support for sickle cell disease (SCD), and realising the many common policies with thalassaemia in addressing the effective prevention and care of SCD, TIF has included coverage of this disorder in the context of its educational programme, which constitutes a major pillar of its work and activities.



Working in official relations with the World Health Organization (WHO) since 1996

In special consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017

Haemoglobinopathies care and cure: Have we reached the end?

John Porter

Professor of Haematology, University College London and Joint Red Cell Unit, UCLH and Whittington Hospitals, London, UK

Recent years have seen accelerating advances in the treatment, monitoring and potential cures for haemoglobin disorders, as the interaction between basic science, pharmaceutical research, and practical medicine intensifies. In order to appreciate how close to the end we may have reached, it is helpful to consider the journey thus far.

For thalassaemia syndromes, advances with non-curative treatment began with the establishment of the principles of blood transfusion and their application in the 1950s both to treat anaemia and suppress erythropoietic expansion. The consequences of transfusional iron overload soon became a problem however, with patients dying in their late teens and early 20s, typically with cardiomyopathy. The introduction of desferrioxamine infusions in the 1970s, led to gradual improvement in outcome and the subsequent introduction and licensing of orally active chelation has contributed to improved treatment adherence and improved survival. Morbidity from iron overload, particularly hypogonadotrophic hypogonadism remains a serious issue and emergence of new pathologies in older patients, such as in the liver, is a cause for concern. Curative treatment with allogeneic stem cell transplantation was introduced in the 1980s but is only available to a minority of patients and is still associated with significant morbidity and mortality. Novel approaches aimed at decreasing transfusion requirements by improving the efficiency of erythropoiesis, such as with activin receptor traps, may prove useful in both transfusion dependent and non-transfusion dependent thalassaemias. Gene therapy is now a reality for a small number of patients and has the potential for application to many patients in whom allogeneic transplant was precluded by lack of a suitable donors, or was too risky for other reasons such increasing as age.

For sickle cell disorders, advances have included the setting up of specialist clinics, pneumococcal septicaemia prevention programs, the application of blood transfusion for the prevention and treatment of disease complications, the use of hydroxyurea for prevention of painful crises and chest syndrome and allogeneic transplantation for carefully selected patients. New pharmacological agents with novel mechanisms of action are being evaluated at a hitherto unprecidented rate. However thus far, the impact of these advances on survival and quality of life in patients as a whole often lags somewhat behind those of thalassaemia. Disease prevention is a key element to management of both sickle and thalassaemia syndromes but implementation has been highly variable both geographically and even between these conditions at a local level. Prevention of births with sickle cell disorders have been less effective than for thalassaemia, even in countries such as the UK which share the same prevention programs for these conditions. The perceived variability and unpredictability of sickle cell disease is part of the reason for this: if all patients had a uniformly fatal outcome without transfusion, blood transfusion would be more uniformly applied, as with TDT , from an early age with perhaps better overall quality of life and survival.

In order approach "the end," advances in therapy will need to be more affordable and deliverable to populations where the conditions are most prevalent. It is anticipated in the next decade that blood transfusion safety will improve, the cost of chelation will fall, the safety and applicability of allogeneic stem cell transplantation with increase, and with further scientific advances such as CRISPR technology, the cost of gene therapy fall. In the meantime, to paraphrase a well-known quotation, "*this is not the end, it is not even at the beginning of the end, but it is perhaps the end of the beginning*".

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Migration: The aftershocks to the provision of healthcare

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Migration is the "movement of people to a new area or country in order to find work or better living conditions" (Oxford dictionary). The term "migration" summarizes forced, reluctant and voluntary migration. Voluntary migration is a comparatively constant event. But reluctant and, in particular, forced migration have been subject to substantial change during the last years. At the end of 2016, more than 17.2 million refugees (+ 5.3 million Palestinians) were on the run outside their home countries. 55% of them fled from Syria (5.5 million), Afghanistan (2.5 million) and South Sudan (1.4 million), respectively. The top hosting countries were not, in fact, the Southern and Western European or North American, but some of the poorest countries in the world. With the refugees from countries where disorders of haemoglobin are very prevalent, the number of patients in the host countries significantly increased within a very short period of time. The extraordinary circumstances required rapid rethinking and adaption and, therefore, did not only pose a big challenge but, in some countries, also a big chance to improve care for patients suffering from hemoglobinopathies.

Although there are certainly several trouble spots in the world, the Middle East crisis was and still is currently the most prominent one. There is a significant prevalence of thalassemia and sickle cell disease among the Syrian and Iraqi population and since the chronically ill were presumably those who left their home countries first, there was a dramatic increase in the prevalence of thalassaemia and sickle cell disease in the host countries. Many patients fled to Western and Northern European countries where hemoglobinopathies were very rare and where the healthcare systems were unable to cope with this sudden increase in patient numbers and complications. For example, disease characteristics were much more pronounced than doctors were used to. Complications occurred that physicians only knew from textbooks. In addition, virtually all families needed significant help in psychosocial matters and many refugees were severely traumatized.

Methods

In addition to an extensive review of the literature, international experts for haemoglobin disorders were contacted via email and asked to take part in an online survey. They were asked if and how relevant migration is for their clinical practise, if they did observe changes in the number of patients during the last five years and if and how they responded to these changes.

Results

The results of this survey are pending and will be presented and discussed at the TIF conference.

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Patients as equal partners in decision-making: The global reality

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Decision making is an inherently complicated procedure, which by its very nature requires the decision-maker to co-opt all the stakeholders concerned. The procedure of decision-making may vary from country to country, depending on its size, culture, history and special demographic circumstances. Around the world, key decision-makers include the executive, the legislature and the judiciary. While the distribution of powers between these three may vary in tandem with their relation to each other, their roles remain the same. While the legislature enacts laws for its citizens, the executive, popularly known as the government, implements these laws and while doing so promulgates policies that are in alignment with the said laws. Mostly, the executive is also authorised to promulgate some laws of its own. The judiciary, on the other hand, comes into the picture when there is a dispute with regard to such laws. It also steps in on its own at times. While settling such disputes, the judiciary also ends up setting what we know as precedents, which also become a part of the legal fabric of a society. In a nutshell, these three are the key decision makers in any country.

As mentioned above, while making decisions, these authorities are mostly required to co-opt all the stakeholders concerned, thereby making decision making a consultative process. These stakeholders include think tanks, research bodies, media and most importantly the affected party. The reason for having such a consultative procedure in place is that the decision makers are not experts in every subject or issue that comes their way. For instance, when a need to promulgate a national policy on thalassemia presents itself to a certain government, whether it be owing to media reportage or representations from the civil society, the decision makers will look towards people considered to be the experts in the subject to come forward and be a part of the policy making. One could say that this sounds like an ideal situation where the government actually invites people concerned with thalassemia to come forward and share views about it for the purpose of policy making. It is, however, true! It is as true for India as it is for any developed country. What we must ensure then is that the government or the decision maker considers us, the patients, as the experts. While it does sound obvious that those impacted with the disorder would be the ones with the first-hand knowledge about the disorder, the very fact that there is a topic in this conference on the role of patients in decision making speaks volumes about the distance that remains to be covered by the patients of thalassemia as far as participation in decision-making is concerned.

With the massive strides in the field of medical science and the unflinching support of organisations like Thalassemia International Federation (TIF), we have now reached the stage where we must step out of the victim mode and represent ourselves before the decision-makers, whether by forming Patients Advocacy Groups or otherwise. One may take cue from various associations around the world. Global HD Organisations are a good example. They are known to have got together to give patients a voice in clinical research. The most popular strategy for reaching out to the decision makers is to unite, engage, and partner both in private meetings and consultative fora like events, task forces and projects. "Unite, Engage & Partner" can therefore be the most successful *mantra* for engaging with the decision makers.

Talking of examples of advocacy and participation by patients, while there are numerous examples in Europe and North America of the power of patient advocacy so much so that patients are on the same level as doctors when it comes to voicing opinions in policy making, TIF on an international level has created since 2009 the Expert Patients Programme, and is now moving forward in giving patients a voice through its educational platform. Recently, India also launched its first Thalassemia Patients Advocacy Group (PAG) in the august presence of the Deputy Chief Minister of the capital of the country. The India PAG has seven patients from the fields of law, psychology, education and IT. The Group is already involved with the government on the formulation of the National Thalassemia Policy. This is a great start and this should give enough and more encouragement to thalassemics across the world to UNITE, ENGAGE AND PARTNER in the process that impacts them the most – decision-making!

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Diagnosis of haemoglobinopathies: New scientific advances

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Abstract

The molecular defects underlying haemoglobinopathies are both deletions and point mutations in the alpha- or beta-globin genes or gene-clusters. To detect point mutations causing alpha- or beta-thalassaemia, direct sequencing is the method of choice to detect the widest spectrum of molecular defects. The most established approach in DNA diagnostics to screen for the most common deletion defects causing alpha-thalassaemia or beta-thalassaemia is gap-PCR, Multiplex Ligation-dependent Probe Amplification (MLPA) and Sanger Sequencing technology to detect breakpoint sequences of previously uncharacterized deletions/duplications. We demonstrate the recent advances in the determination of duplications and deletions causing alpha- or beta-thalassemia, using Next Generation Sequencing, array Comparative Genome Hybridization and Target Locus Amplification.

We present three cases in which the use of advanced technologies allow the diagnosis of unexpected disease genotypes.

Introduction

The thalassaemias are a diverse group of disorders of haemoglobin synthesis, all of which result from a reduced output of the alpha- or beta-globin chains of the adult haemoglobin. Despite the great technological advances in mutation detection, the screening of haemoglobinopathies still requires the combined use of haematological and molecular techniques to arrive at an accurate diagnosis. Specialist knowledge is required of genotype/phenotype relationships because of the multitude of complex phenotypes which result from interactions between genotypes and co-inherited globin gene disorders. Recent advances in technology, such as array Comparative Genome Hybridization (aCGH), Target Locus Amplification (TLA) and Next Generation Sequencing (NGS), may help to determine deletion/duplication breakpoints to the sequence level, and provide more insight in rare disease mechanisms.

The NGS approach is now embedded in many genomic laboratories to detect small sequence changes, but is less adapted to determine structural variants because of the relatively short sequence reads. Target enrichment methods, such as bait capture, are used to obtain more of the breakpoint spanning fragments and use NGS more effective (Clark *et al.* 2017, 2016). Mechanically sheared genomic DNA is used to create a library of adapter containing fragments (Agilent SureSelect Library preparation), hybridised to biotinylated RNA probes designed to hybridise fragments from the region of interest, selected by streptavidin coated magnetic beads and subsequently subjected to Illumina sequencing (MiSeq).

The arrayCGH cytoscan HD array (Affymetrix, Thermo Fisher Scientific, Santa Clara, CA) contains ~2.67 million markers of which ~743000 SNP probes and ~1950000 copy number probes (average spacing 1 probe per 1.1 kb). ArrayCGH technology has been embedded in the cytogenetic lab as a tool to visualize deletions which otherwise are not detectable by microscopic investigation or difficult to detect by FISH analysis. Array CGH has largely replaced these techniques in the genetic lab. By looking at SNP's on the array a distinction can be made in large deletions in chromosomes of paternal or maternal origin.

Targeted sequencing by proximity ligation is used for comprehensive variant detection and local haplotyping. TLA works without prior knowledge of the locus of interest other than the specific primer sequence information necessary to design inverse PCR primer set to amplify and sequence tens to hundreds of kilobases of surrounding DNA. This enables the detection of single nucleotide variants, deletion/duplication/inversion breakpoint sequences and local haplotyping of neighbouring stretches of DNA, which have been cross-linked, digested and ligated to form anchor-containing DNA circles amplified by inverse PCR. The library obtained is subsequently sequenced by NGS (de Vree *et al.* 2014).

Materials and Methods

Patients EDTA blood samples were collected and analysed by standard haematological and biochemical methods. The Hb fractions were separated by HPLC (Trinity Biotech, Menarini) and Capillary Electrophoresis (Capillarys Flexpiercing, Sebia, France). DNA was isolated from leucocytes and samples diluted to a standard concentration of 50 ng/ul.

MLPA kit P140C2 and P102B (MRC-Holland, Amsterdam) were used to detect rearrangements in the alpha- and beta-globin gene clusters resp.

Next Generation sequencing was partly performed in King's College London (MiSeq, Agilent Sure select) and partly in Leiden (HiSeq, GenomeScan, Leiden, The Netherlands). ArrayCGH was performed using the Cytoscan HD array (Affymetrix, Thermo Fisher Scientific provides, Santa Clara, CA, USA); 250ng of DNA was used in the CytoScan™ Automated Target Preparation Solution on NIMBUS™. The array-chip contains ~2.67 million markers of which ~743000 SNP probes and ~1950000 copy number probes (average spacing 1 probe per 1.1 kb).

TLA technology was used from Cergentis BV (Utrecht, NL) and NGS was performed at the Leiden Genome Technology Center (LTGC, Leiden, NL).

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Results

Case #1. This was a collaborative study of Barnaby Clark, Claire Shooter and Swee Lay Thein (King's college, London) in which a family of Syrian ancestry was studied. Mother was a carrier of HBB:c.135delC (cd44(-C)), father showed normal haematology and CE/HPLC results. Two daughters were shown to carriers of beta-thalassemia, but the haematology was more severe than seen in the mother. MLPA analysis revealed a duplication of the alpha-globin gene cluster including the Major Conserved Regions 1 to 4. To determine the orientation of the duplication (head-head, head-tail or tail-tail or translocated) and determine if any intervening sequences between the duplication breakpoints were present, an enrichment step was introduced making a fragment library using bait capture by biotinylated RNA oligo's specific for the alpha-globin gene region, followed by Next Generation Sequencing using the Illumina MiSeq. After breakpoint primers were designed the amplified fragment was sequenced to contain the breakpoint. A head-to-tail arrangement was determined with three ambiguous basepairs between the two duplicated segments of 120,500 bp in length (Clark *et al.* 2016, 2017).

Case #2. A female born as a healthy carrier who inherited just the HBB:c.315+1G>A (IVS2-1g>a) beta-thalassemia mutation from her father presented with a transfusion dependent beta-thalassemia major phenotype later in life. The DNA analysis showed a mosaic for an almost complete hemizygosity for the mutated allele from father. Array-CGH using an array-chip containing ~2.67 million markers of which ~743000 SNP probes and ~1950000 copy number probes (average spacing 1 probe per 1.1 kb), showed the presence of a 5Mb deletion (1,313,791-6,287,277; hg19 / grch37) on the tip of the short arm of chromosome 11, which takes away the maternal allele containing the normal beta-globin gene, alongside with other genes among which the maternally imprinted erythrocyte growth factor (EGF-1) and H19 genes. The mosaic presence suggests a somatic event and the deletion of the maternal allele may explain the growth advantage of cells containing the deletion and the mutated beta-gene in hemizygosity (Traeger-Synodinos *et al.* manuscript in preparation).

Case #3. A Dutch Caucasian family with a novel alpha0-thalassemia deletion was found by haematological and MLPA analysis. The deletion was between 10 and 20 kb based on MLPA results. Targeted Locus Amplification (TLA, Cergentis) was used in combination with capture baits designed to recognize fragments from the alpha- and beta-globin gene clusters to enrich for the breakpoint fragment in isolated DNA of the carrier, followed by NGS. The breakpoint sequence was confirmed by designing gap-PCR primers and subsequent amplification and direct sequencing of the breakpoint fragment. This novel alpha0-thalassemia deletion is called —Jc, it is 16.7 kb in length involving the HBM, HBA1 and HBA2 gene (NG_000006.1:g.151901_168673del16772). (Harteveld *et al.*, manuscript in preparation).

Discussion

The molecular defects underlying these disorders are both deletions and point mutations in the alpha- or beta-globin genes or gene-clusters. To detect point mutations causing alpha- or beta-thalassaemia, direct sequencing is the method of choice to detect the widest spectrum of molecular defects. The most established approach in DNA diagnostics to screen for the most common deletion defects causing alpha-thalassaemia or beta-thalassaemia is gap-PCR, Multiplex Ligation-dependent Probe Amplification (MLPA), and automated Sanger sequencing. The new technologic advances such as micro-array and Next Generation Sequencing technology make possible new scientific advances in the identification of disease mechanisms involved in haemoglobinopathy. This is demonstrated by three cases presented.

Complex interactions involve duplications of the alpha-globin gene cluster which by overexpression of the alpha-globin genes influences the disease phenotype in beta-thalassemia carriers expressing a beta-thalassaemia intermedia. Recent advances in technology including Next Generation Sequencing (NGS) were used to characterize the duplication breakpoint.

Late onset beta-thalassemia is an extremely rare phenomenon, in which a healthy beta-thalassemia carrier develops a transfusion dependent thalassaemia intermedia during life. DNA analysis reveals a mosaic loss of heterozygosity in the majority of blood cells which is absent in DNA isolated from hair or buccal cells. This is suggestive of a somatic deletion of the wild type maternally inherited beta-gene in a (subset of) hematopoietic stem cell(s) which gradually replaced the heterozygous cells in time. By using array Comparative Genome Hybridization (aCGH) the deletion length, the level of mosaicism and the positioning of the deletion to the maternal chromosomal could be identified.

In the last example, we presented a novel technology used to enrich for fragments containing the deletion breakpoint of a rare novel deletion found in a family of Dutch origin. Target Locus Amplification (TLA) was used to crosslink neighbouring DNA stretches surpassing tens to hundreds of kb, in order to target the deletion breakpoint by inverse PCR and subsequent Next Generation Sequencing.

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New challenges in diagnosis of haemoglobinopathies: Migration of populations

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Abstract

The current influx of economic migrants and asylum seekers from countries with a high prevalence of haemoglobinopathies creates new challenges for health care systems and diagnostic laboratories. The migration of carriers introduces new and novel haemoglobinopathy mutations to the diagnostic repertoire of a laboratory, often creating new pressures to improve and update the carrier screening technology and diagnostic scope. For antenatal screening programmes, the marriage of partners from different ethnic groups can lead to the risk of compound heterozygote children being born novel mutation combinations, creating problems in the provision of accurate advice regarding the expected phenotype of the thalassaemia or haemoglobinopathy disorder. In the UK, the impact of immigration required the National Haemoglobinopathy Reference laboratory to change the strategy and techniques used for the molecular diagnosis of thalassaemia and the haemoglobinopathies. In 2005, due to the increasingly large range of β-thalassaemia mutations that needed to be diagnosed, the laboratory switched from a three-step screening procedure using ARMS-PCR to a simpler but more expensive one-step strategy of DNA sequencing of the beta and alpha globin genes for all referrals. After ten years of employing this strategy, a further 57 novel thalassaemia and haemoglobinopathy alleles were discovered (11 new β-chain variants, 15 α-chain variants, 19 β-thalassaemia mutations and 12 α^+-thalassaemia mutations), increasing further the extremely heterogeneous spectrum of globin gene mutations in the UK population.

Introduction

The haemoglobinopathies are a group of autosomal recessive disorders characterised by either a reduced synthesis of one or more normal globin chains (the thalassaemias), the synthesis of a structurally abnormal globin chain (the haemoglobin variants) or in a few cases by both phenotypes (the reduced synthesis of a Hb variant, *e.g.* Hb E). As a group they are the most common single gene disorder in the world and are found at high frequencies in many populations worldwide where falciparum malaria has been or still is prevalent, due to carriers being protected against dying from malaria. More than one thousand different mutant alleles have at the molecular level, as described in several databases such as HbVar [1] and IthaGenes [2]. The mutations are regionally specific, dividing into four groups of countries: Mediterranean, Asian Indian, Southeast Asian, and sub-Saharan African. Each country in its group has a spectrum of abnormal haemoglobins and thalassaemia mutations, consisting of a few common alleles and a larger number of alleles found at much lower gene frequencies. The spectrum and frequency of haemoglobinopathy mutations, especially those for β-thalassaemia, have now been determined for most countries [3].

Haemoglobin disorders also occur in the native populations of some non-malarial countries, *e.g.* most Northern European countries, but are found at such low gene frequencies that thalassaemia and sickle cell disease were not a health problem until the last century when migration from endemic areas began to introduce these disorders to most of Northern and Western Europe. For the UK, the major immigrant populations groups were: Indian, Afro-Caribbean, Pakistani, African, Bangladeshi, Cypriot, Italian and Chinese. An early study of the haemoglobinopathy mutations found in these UK consisted of a group of very rare ones specific to individuals of white British origin, such as those with a dominant β-thalassaemia phenotype, or they were mostly one of the more common mutations observed in one of the four regionally specific groups of countries described above [4].

During the last twenty years, official national statistics reveal that immigrants to the UK have come from many different countries as they flee from civil wars and military dictatorships, in particular Zaire, former Yugoslavia, Nigeria, Somalia, Sri Lanka, Iran, Syria, Iraq and Afghanistan. These new immigrant populations pose new problems for the molecular screening of β-thalassaemia mutations, as the spectrum and allele frequencies of the mutations had not been determined for some of these populations, such as the Kurdish refugees. Thus a quick screen for β-thalassaemia mutations by the cheap method of ARMS-PCR was not possible for patients from Afghanistan and Iraq, and it was found that an ever increasing number had to have a molecular diagnosis by direct sequencing of the DNA. For this reason, in 2005 the laboratory changed its molecular screening strategy for β-thalassaemia from a three-step screening procedure using ARMS-PCR [5] to a simpler but more expensive one-step strategy of routine DNA sequencing of the for β-globin genes for all referrals.

Methods

Blood samples of patients identified as presumptive haemoglobinopathy carriers using haematological techniques for the national antenatal screening program, were referred to the National Haemoglobinopathy Reference Laboratory for diagnostic confirmation and genotype identification. Each blood sample was subjected to a full blood count and quantitation of the Hb F and Hb A_2 by high performance liquid chromatography system using a Bio-Rad Variant

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1 analyser. Presumptive identification and quantification of abnormal haemoglobins was carried out by both HPLC and isoelectric focusing gel electrophoresis. The HPLC retention time was recorded for each Hb variant peak and the isoelectric focussing distance from Hb A was measured against known control Hbs [6].

In 2005 the molecular diagnostic strategy was changed from screening for by ARMS-PCR to routine screening of the β-globin gene. To simplify the diagnostic strategy, it was decided to also amplify the α-globin genes routinely on all referred samples in addition to routinely screening for deletion mutations by gap-PCR or MLPA. Since the change in diagnostic strategy, approximately 12,000 DNA samples underwent PCR to selectively amplify the β-, α1- and α2-globin genes [7]. The PCR products were cleaned up and quantified by gel electrophoresis before being subjected to cycle sequencing. The forward and reverse sequencing products were then analysed using an ABI-PRISM 3130 automated DNA analyser.

To complete the routine molecular investigations, each sample was analysed for the common 3.7 and 4.2 kb single α^+-thalassemia globin gene deletion mutations by multiplex gap-PCR [8]. When necessary, samples were screened for larger α- and β-globin gene cluster deletions by gap-PCR or MLPA to investigate the possibility of α^0-thalassemia, δβ-thalassemia, deletional HPFH, εγδβ-thalassemia, Hb Lepore, Hb Kenya and deletional β-thalassemia as previously described [9]. DNA samples that tested negative for α^+-thalassemia and associated with an MCH below 25pg were routinely screened for α^0-thalassemia, and samples associated with an elevated Hb A_2 or raised Hb F and a normal β-globin gene sequence were screened for β-globin gene cluster deletions.

Results

Carriers were investigated originally using a three-step diagnostic strategy in which the common β-thalassaemia mutations were screened for first by the amplification refraction mutation system ARMS-PCR with panels of primers for the common mutations, and if negative results were obtained, screened for a second time by ARMS-PCR for the rare mutations for each major ethnic group. Then any remaining uncharacterised samples were analysed by targeted DNA sequencing to identify a very rare or novel thalassemia mutation not included in the primer panels. This strategy was very successful and revealed a total of 68 different β-thalassemia mutations and 29 non-deletional α^+-thalassemia mutations in the UK population [5]. A comparison of the UK spectrum of mutations to those published for 59 other countries showed that the UK had the largest number of different β-thalassaemia and non-deletional α^+-thalassemia mutations.

Since 2005, more than 12,000 carriers for the antenatal screening programme have had their β-globin gene and α−globin genes sequenced routinely by the new carrier diagnostic strategy. This has resulted in the discovery of 60 novel thalassemia and abnormal haemoglobin mutations over a period of ten years. These consisted of 11 novel β-chain variants, 15 α-chain variants, 19 β-thalassaemia mutations (Table 1) and 15 non-deletional α^+-thalassaemia mutations (Table 2) [7]. The discovery rate of novel mutations each year appears to be constant, with 29 found in the first five years and 31 in the second five year period, reflecting a continual influx of new immigrant populations to the UK over the ten year period. The large number of new thalassemia alleles discovered confirms the wide racial heterogeneity of mutations in the UK immigrant populations. This data has increased the number of known thalassaemia mutations diagnosed in UK patients to 99 different β-thalassemia point mutations, and 62 non-deletional α^+-thalassemia alleles. In addition, it has resulted in an Hb variant library of 265 Hb Variants characterised by their DNA sequence, HPLC retention time and iso-electric focussing position.

The continual increase in the spectrum of known mutations is driven by the changing demographics of the UK immigrant population, with new ethnic groups such as Kurds and Iraqis entering

Table 1. Novel β-thalassaemia mutations and some haematological findings.

Mutation	HGVS	MCV fl	MCH pg	Hb A2 %	Hb F %	Type	Ethnic Origin
-88 (C→G)	HBB: c.-138C>G	78.3	21.7	5.6	5.0	β+	British
-71 (C→T)	HBB: c.-121C>T	63.8	20.0	5.5	5.1	β+	Unknown
-30 (T→G)	HBB: c.-80T>G	71.7	23	4.9	10.2	β+	Unknown
Codon 5/6 (-TG)	HBB: c.18_19delTG	64.0	19.9	5.6	1.7	β	Turkish
Codon 72/73 (+T)	HBB: c.219_220insT	65.6	19.7	6.1	0.6	β	British
Codon 90 (-G)	HBB:c.271delG	65.0	20.3	2.6	21.7	dominant	Lithuanian
IVSII-2 (-TGAGTCTATGGG)	HBB: c.315+2_315+13del TGAGTCTATGGG	67.0	21.3	4.9	1.6	β+	British
IVSII-781 C→G)	HBB: c.316-70C>G	85.0	26.4	4.4	1.1	β+	African
IVSII-848 C→T	HBB:c.316-3C>T	85.0	28.1	3.0	1.3	β+	Unknown
Codon 114 (+TGTGCTG)	HBB: c.345_346insTGTGCTG	64.0	19.6	5.4	1.0	β	Irish
Codon 117 (-C)	HBB: c.354delC	69.0	20.7	3.8	6.3	dominant	British
Codon 124/125 (+A)	HBB: c. 375_376insA	67.0	20.4	5.0	1.9	β	Unknown
Codon 125 /126 (-CCAGTG)	HBB: c.376_381delCCAGTG	78.0	26.0	3.7	9.6	dominant	British
Codon 130 (T→A)	HBB: c.393T>A	68.0	17.4	3.5	1.4	β	Unknown
Codon 131 (+A)	HBB: c.394_395insA	63.5	19.3	4.7	2.0	β	British
Codon 131 CAG→TAG	HBB:c.394C>T	73.1	23.3	5.7	5.0	dominant	British
3' UTR (+C, -TGGATTCT)	HBB: c.*+95_*+107delinsC	61.0	18.5	6.0	1.5	β+	British
Poly A (-AA)	HBB: c.*+111_*+112delAA	73.6	23.9	4.0	0.5	β+	British or Irish
Poly A (A→T)	HBB: c.*+112A>T	80.0	25.5	4.9	0.5	β+	African

Table 2. Novel α⁺-thalassaemia mutations and some haematological findings.

Mutation	HGVS	MCV fl	MCH pg	Hb A_2 %	Hb F %	Ethnic origin
α1 IVSI-I (G→C)	HBA1:c.95G>C	69.9	23.3	2.5	0.9	Middle East
α1 Codon 104 (TGC→TGG) [Cys®Trp]	HBA1:c.315C>G	79.0	24.8	3.4	0.2	Pakistani
α1 Codon 108 (-C)	HBA1:c.328delC	72.0	24.3	2.9	0.7	Egyptian
α1 Codon 124-128 (-13bp)	HBA1:c.333_345del	71.0	21.1	2.4	0,2	Pakistani
α1 Poly A (G→A) (AATAAAG→AATAAAA)	HBA1:c.*+95G>A	73.4	24.0	2.7	1.0	Pakistani
α2 Initiation codon translation sequence (-1bp)	HBA2:c.-3delA	73.0	23.1	2.4	0.3	Indian
α2 Initiation codon (T→G) (ATG→AGG)	HBA2:c.2T>G	75.3	23.6	2.9	3.2	Middle East
α2 Initiation codon (A→T) (ATG→TTG)	HBA2:c.1A>T	79.4	23.3	2.4	0.3	Southeast Asian
α2 Codon 37 (-C)	HBA2:c.114delC	77.0	26.5	3.0	0.1	British
α2 Codon 47 (-A)	HBA2:c.143delA	71.3	22.6	2.8	0.3	Unknown
α2 Codon 47/48 (-ACCT)	HBA2:c.143_146delACCT	75.0	24.1	2.3	0.4	British
α2 Codon 51/52 (+G)	HBA2:c.156_157insG	67.0	22.4	2.9	0.8	Unknown
α2 Codon 73/74 (-GTGG)	HBA2:c.220_223delGTGG	68.5	21.5	2.7	0.3	Indian
α2 Codon 101 (CTA→CCA) [Leu→His]	HBA2:c. 305T>C	68.0	23.0	2.9	0.4	Irish
α2 Codon 56 (-AA)	HBA2:c. 169_170delAA	75.4	24.2	2.8	0.3	Unknown

the country from war zones in the Middle East, and migrants coming to the UK for temporary work from countries such as nurses from the Philippines. The impact of migration from such areas has increased significantly the range of haemoglobinopathy mutations that need to be detected in UK patients and increases the number of possible combinations and interactions of the different mutations. This creates counselling problems, as the phenotypes of these new genotype combinations have not been reported before, thus making it difficult to give accurate advice regarding outcomes in prenatal diagnosis cases. An example of this was a couple from the Philippines at risk of having a child with β-thalassaemia with the compound heterozygous phenotype of the frameshift mutation codon 67 (-TG) [c.202_203delGT] and a novel β⁰-thalassaemia, a combination for which there was no published information which could be used to inform the parents of the probable phenotype – thalassaemia major or intermedia?

Conclusions

The impact of migration of haemoglobinopathy carriers from endemic areas to a non-malarial country increases significantly the range of haemoglobinopathy mutations that need to be detected and increases the number of possible combinations and interactions of the different mutations. Thus molecular diagnostic laboratories in such countries must have the technical expertise, equipment and diagnostic strategy to detect a large variety of mutations quickly for prevention programmes based on carrier screening and prenatal diagnosis. They must also have the ability to change and adapt the molecular diagnostic strategies and technologies to address the increasing variety of mutations encountered. They must also able to provide advice on the clinical and genetic consequences of the finding novel compound genotypes from new immigrant ethnic groups for which there may be little or no published information regarding the genotype-phenotype relationship. Thus another impact of immigration on carrier screening is a requirement for staff to maintain an up to date knowledge of the thalassaemia mutations and their genotype-phenotype relationships for all ethnic groups.

The impact of migration is a driver for changing carrier screening diagnostic strategy and technology. In the UK, new immigrant populations such as the Kurds, Afghanis and Iraqis entering the UK posed problems for the molecular screening of β-thalassemia mutations which were met by changing the diagnostic strategy and molecular diagnostic technology from ARMS-PCR to routine Sanger DNA sequencing of the α-globin and β-globin genes in every sample. Analysis of the results after ten years of screening have revealed a large increase in the variety and spectrum of thalassaemia and haemoglobinopathy mutations in the UK population, confirming that the change in the screening strategy and technology was timely and necessary.

In the future, the impact of immigration will continue to drive forward changes in carrier screening strategy and technology. Indeed, a strategy of carrier screening by simply sequencing the whole alpha and beta globin gene clusters by next generation sequencing without any haematological screening has already been shown to be possible in a high-prevalence Chinese population. The authors claimed that NGS sequencing on its own was an improvement over haematological screening, no carriers were missed and some carriers were identified for which haematological screening would have diagnosed as normal [10]. However it was concluded that knowledge of haematological screening data and Hb pattern analysis data was still required in order to understand the importance of some of the globin gene DNA sequence changes revealed by the next generation sequencing data and thus the best carrier screening practice in the future will still require a combination of a patient's haematological data and Hb pattern analysis and a knowledge of thalassaemia and Hb variant genotype-phenotype relationships in addition to the patient's genomic sequence data.

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Informed choice in a multicultural world

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Knowledge and autonomy are key aspects of informed choice; it is important to define what is important for participants to understand, when accepting or declining screening and for individuals to understand that screening is optional and their own personal choice

There are no agreed thresholds or minimum standards for the knowledge an individual is required to have to make an 'informed' choice. It is time that minimum agreed standards are developed for practitioners who provide genetic information.

There is no standard for evaluating good knowledge or informed choice in population reproductive genetic screening, however measuring people's choices is a good indicator of informed choice.

Informed choice in a multicultural world will be explored and an overview of the different levels of informed choice, practiced in the pathway from genetic screening to identifying at risk couples discussed.

Genetic counselling and informed choice

Genetic counselling is complex and is inseparable from medical diagnosis and aims to increase people's control of their own health and their family's health by informing them of the resources available for diagnosis and treatment and prevention. Genetic counselling is particularly important in medical genetics because of the often predictive nature of genetic information and the difficult choices people have to make.

Genetic counselling has been defined "The process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, and the probability of developing and transmitting it and the ways in which this may be prevented or ameliorated" (1)

Genetic counselling requires, a correct diagnosis in the presenting family member,

explanation of the nature and prognosis of the disorder, the treatment available and where to find it, estimation of genetic risk for parents and family members. This requires drawing a family tree. It may also call for investigations on other family members. It requires communication of genetic risks and the options for avoiding them, including the chances of parents and other family members passing the disorder on to their children, and an explanation of that risk. The options for avoiding further affected children must also be addressed, including techniques of prenatal diagnosis and preimplantation genetic diagnosis if it is available and associated risks including risk of error and pregnancy complications. It requires the support for the individual or couple in making the informed decision that is right for them and accessibility for long-term contact: people at risk often need counselling and support at several points in their life.

Therefore the genetic counsellor will need the skill and specialist knowledge to communicate this information, so that the individual/couple can make their informed choice. The core ethical principles of genetic counselling include; the individual/couples right to full information, the autonomy of the individual or couple and strict confidentiality (2). Information is the main therapeutic intervention in medical genetics and misinformation is the main risk. Medical training rarely equips doctors to provide adequate genetic counselling and to discuss complex issues with their patients. The responsibility involved in genetic counselling should not be underestimated. Counselling is understanding a set of facts and effectively communicating them to the individual/couple. Therefore when counselling couples who at risk for haemoglobin disorders, it is essential that non-directive counselling is used, the couples must learn the facts, think through the issues and reach a decision they can live with for the rest of their lives, there is 'no right choice'. The choice made is determined my many factors, which the counsellor must take into account, including family and reproductive history, social religious and cultural attitudes, personal experiences, economics, educational level and their understanding of their risk.

A recent lawsuit against a health care provider in Oregon highlights the importance of genetic counselling, in times where test access is becoming easily accessible. In this case a variant of unknown significance was misinterpreted by the health care providers as pathological and the woman subsequently underwent a double mastectomy and hysterectomy (3).

Screening policies

People's options are influenced by the stage in life when they are informed of their genetic risk and whether prenatal diagnosis is available. Table 1 summarises three screening policies. If the risk is identified prospectively *i.e.* before the birth of an affected child *i.e.* pre-marital, then all the available options are available to the couple, as they can choose to separate and find a non-carrier partner, they can choose to have no children, to take the chance to have children as usual and restrict family size in the hope they will not have affected children, or to use prenatal diagnosis (PND) and selective termination of affected pregnancies, if it is acceptable and available. Pre-pregnancy screening limits choices, as the choice to separate is not available and antenatal screening limits choices even further.

Unless an active screening programme is available, it is unusual for a couple to learn of their risk of having children with a haemoglobin disorder before marriage and most couples learn of their risk when an affected child is diagnosed *i.e.* retrospectively identified to be at risk.

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Experience with screening programmes

It is often thought that affected births can be prevented, if at risk couples are identified prior to marriage, on the assumption that they will separate and find a non-carrier partner. However in many societies, marriage is a complex phenomenon that may involve many family members besides the couple themselves and marriage partners are selected either because of a strong personal preference, or family or traditional reasons. If a planned marriage is called off it can cause social embarrassment or stigma for the young people and their families.

Before prenatal diagnosis became available marriage between carriers in Cyprus was actively discouraged, however this proved very unacceptable to the population and was soon abandoned 'because of evasions' (4,5). Soon afterwards, mandatory premarital screening became available amongst the Greek Cypriots by the Greek Orthodox Church and among the Turkish Cypriots by the civil authorities. It was found that 98% of at risk- couples proceeded to marry and the majority used prenatal diagnosis and selective termination of affected pregnancies and consequently very few children with thalassaemia are born in Cyprus. In Cyprus, Italy and Greece the populations are well informed about thalassaemia and there has been a large fall in the birth of affected births in these Mediterranean countries (6). The outcome of the high uptake of prenatal diagnosis by couples at-risk for thalassaemia in Mediterranean countries, reflects the at risk community's view of the heavy burden of the disease and its treatment. However, things can change as treatment becomes more effective and acceptable and the uptake of prenatal diagnosis may fall if new approaches like preimplantation genetic diagnosis become easier and more widely available, then the burden of prevention may decline and uptake may rise.

Mandatory premarital screening for sickle cell and thalassaemia has been implemented in several Muslim Countries (Table 2), however it is important to discuss the acceptability of these services and the availability of the option of prenatal diagnosis and selective ter-

Table 1. Choice of screening programme.

Screening policy	Options for at risk couples identified	Advantages	Limitations
Pre-marital screening	1. Separation /partner choice 2. Restrict family size 3. PND/ TOP if affected 4. Neonatal diagnosis, optimal care	Permits informed choice among all available options	1. Limited to unmarried couples. Takes over 20 years to full effect if married couples not included. 2. Infrastructure for premarital screening may not exist. 3. Uptake of service may belimited.
Pre-pregnancy screening	2. Restrict family size 3. PND/ TOP if affected 4. Neonatal diagnosis, optimal care	Targets all couples planning a pregnancy.	1. Infrastructure for pre-pregnancy screening may not exist. 2. Uptake of service may be limited.
Antenatal screening	3. PND/ TOP if affected 4. Neonatal diagnosis, optimal care	1. Infrastructure (maternity services) exists 2. Can detect all at-risk pregnancies	1. Ethical only if PND with option of TOP available. 2. Choice limited to PND/TOP or neonatal diagnosis. 3. Risk often detected too late for option of PND/TOP.

Table 2. Experience with screening programmes.

Country/region	PND available	TOPavailable	Cancellation of marriage %	Fall in affected births %
UK	Yes	Yes		40-50
Cyprus	Yes	Yes	<5	Nearly 100
Italy	Yes	Yes	<5	Large
Greece	Yes	Yes	<5	Large
Turkey	Yes	Yes	13	90
Iran	Yes	Yes	<10	80-90
Palestine	Yes	No	-	-
Jordan	Yes	*No	3-40	-
Saudi Arabia	No	No	10	-
Bahrain	Yes	Yes	58	-
Iraqi Kurdistan	Yes	Yes	2	65
Ras Al Khaimah, UAE	No	No	0	-
India	No national programme. Some states? Premarital. Some Students			
Pakistan	No national strategy. Regional: Punjab			
Bangladesh	No programme			

*Although is available in some centres.

mination of affected pregnancies. From a Muslim perspective, it is considered ethical to perform a termination to protect a woman's life or health, or because of a fetal abnormality incompatible with life (7). However, the stage at which termination may take place seems to vary, some Muslim jurists do not allow abortion at any stage, whilst others would permit termination in the first 120 days of fetal life, where there is a reason, such as danger to the mother or the fetus. However some jurists would only allow termination at 40 days and others at 90 days. Termination of pregnancy is absolutely prohibited after the soul is breathed into the fetus after 120 days of fetal life. Muslim theologians regard foetal development as occurring in three stages, each lasting 40 days: the sperm cell and ovum, the clump resembling a blood clot and the lump of flesh (foetus). At the end of these stages, the fetus is ensouled. However, the belief that ensoulment occurs only after120 days does not change the fact that life starts at a much earlier stage of the embryo's development. (8).

The objective of premarital screening programmes in Middle East countries where termination of pregnancy is illegal, is to reduce the prevalence of beta thalassaemia through genetic counselling and to discourage at-risk marriages,

Mandatory premarital screening was implemented in Saudi Arabia in 1994, with the objective of decreasing at-risk marriages. However' following counselling almost 90% of couples married, despite being aware of their risk and being actively discouraged from marrying. The option of prenatal diagnosis is not generally available in Saudi Arabia (9). More recent data from Saudi Arabia would suggest that the majority of at-risk couples still precede to marry following premarital screening. A cross sectional study by Sulaiman et al, looked at three groups: general population, couples presenting for premarital screening and couples who had received their premarital screening results. They found that nearly 70% of the general population felt that at-risk couples should not be allowed to marry. However they also found that 90% of couples proceeded to marry (10)

Iran, a large country in the Eastern Mediterranean region, has a comprehensive primary health care system capable of reaching every family, which incorporates regular in-service staff training. The majority of affected thalassaemia patients are diagnosed and every effort is made to provide the best possible treatment, significantly improving survival rates. As a result, the number of thalassaemic patients under treatment was increasing by about 1,200 per year with over 20,000 attending dedicated treatment centres. The costs of optimal treatment (11) was about $150 million a year, equivalent to almost 8% of total national health expenditure. If the trend continued, future costs could rise to over half the national health expenditure. As this is obviously unfeasible, a national programme providing premarital genetic screening, genetic counselling and prenatal diagnosis was developed. Following a careful pilot study, premarital thalassaemia screening was introduced in 1997 (12). The results were considered at the highest medical and political levels, where they were understood to represent the verdict of the people, and a fatwa was issued permitting termination of pregnancy up to 120 days fetal life, when a fetus is confirmed as having a serious disorder. For reasons of cost efficiency and to reduce the possible stigma for women, many centres test the man first, only testing the woman if his result is positive. Prospective couples that are both carriers see a trained health worker, usually a doctor for counselling. The programme is conducted according to the ethical principles of autonomy, full information and confidentiality and allows informed choice.

Annual statistics on outcomes returned by district health centres to the Ministry of Health indicated in the early years of the programme, when prenatal diagnosis

was only available through a private clinic in Tehran, only 50% of couples identified at risk proceeded to marry. However since 2000 the figure has increased steadily. The most recent figures show that in follow up of 75% of at at-risk couples, that the separation rate is less than 10% and 82-92% of couples utilize prenatal diagnosis and of those 96% of women terminate an affected pregnancy (Ashraf Samavat personal communication). This is thought to reflect the spread of the policy of non-directive counselling and knowledge of the availability of prenatal diagnosis. A national network of DNA diagnostic laboratories is available making prenatal diagnosis accessible to all within the national health system (13). The Iranian prevention programme represents a programme where a fully informed choice is possible. Consequently there has been a more than 80% fall in affected thalassaemia major births (14).

Egypt has also been offering prenatal diagnosis to at-risk couples from some centres. There is no national programme and the majority of couples are retrospectively identified. El Beshlawy et al showed that by having an in depth discussions with the parents when an affected fetus was diagnosed, following prenatal diagnosis and focussing on the religious aspects of termination of pregnancy and the religious fatwa, which permits termination of pregnancy up to 120 days of fetal life when the fetus has a severe fetal abnormality: 100% of the mothers opted to terminate their pregnancy (15).

In Pakistan where annually over 5000 children with beta thalassaemia are born (16), there is no national prevention programme. Prenatal diagnosis was first introduced in 1994 in Pakistan by Dr Suhaib Ahmed (17,18). Before initiating the service, it was considered important to seek the views of religious scholars. Two renowned religious scholars in Pakistan gave a clear verdict permitting termination of pregnancy before 120 days of fetal life, where the foetus is indicated as having a serious disorder.

The majority of couples undergoing prenatal diagnosis in Pakistan already have an affected child. Since 1994 Dr Ahmed's centre has performed over 23.000 prenatal diagnoses for thalassaemia and over 90% of women terminate affected foetuses, however there has been little impact on the birth prevalence of thalassaemia in Pakistan, as the majority of these couples already have an affected child. Recently regional premarital screening has being offered in the Punjab area in Pakistan, it will be interesting to follow the results of such a programme.

Other programmes are shown in Table 2, in most countries where premarital screening is offered, the majority of at-risk couples go ahead and marry. The fall in affected births in countries where prenatal diagnosis and selective termination is available is high (19).

The UK Sickle cell and Thalassaemia screening programme was introduced in 2000. It is based on antenatal screening (20). The programme aims to identify carrier women by 10 weeks gestation and to offer prenatal diagnosis to at- risk couples by 12 weeks gestation with the aim of carrying out prenatal diagnosis by 12 weeks 6 days. However with antenatal screening the choice for women is limited, it is either prenatal diagnosis with selective termination of an affected fetus or neonatal diagnosis. Often at risk couples are identified late, Modell et al showed very early on that the uptake of prenatal diagnosis decreased amongst the British Pakistan population, when offered in the second trimester of pregnancy (21). Recent data from the screening programme also shows that the number of women terminating affected pregnancies for both sickle cell and thalassaemia decreases with increasing gestational age (22), highlighting the importance of early detection, counselling and offer of prenatal diagnosis. Also highlighting the importance of identifying at least women before a pregnancy and offering them counselling and advice on partner testing when planning children, or as soon as a pregnancy is confirmed.

Conclusions

Informed choice requires clear and accurate information. Informed choice is dependent on the time in life the information is provided. The multicultural world limits choices for at-risk couples. Without PND and legal termination of pregnancy premarital screening will only succeed if couples separate. Existing programmes show that marriage cancellation is low. Fully informed choice can only be achieved with the availability of PND and legal termination of pregnancy.

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Diagnostic strategies in hemoglobinopathy testing, the role of a reference laboratory in the USA

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Abstract

Although commonly assessed in the context of microcytosis or sickling syndrome screening, hemoglobin mutations may not be as readily considered as a cause of other symptoms. These include macrocytosis with or without anemia, chronic or episodic hemolysis, neonatal anemia, erythrocytosis, cyanosis/hypoxia and methemoglobinemia/sulfhemoglobinemia. Hemoglobin disorders commonly interfere with the reliability of Hb A1c measurement. Because the clinical presentation can be varied and the differential diagnosis broad, a systematic evaluation guided by signs and symptoms can be effective. A tertiary care reference laboratory is particularly challenged by the absence of pertinent clinical history and relevant laboratory findings, and appropriate use of resources in a data vacuum can be problematic. To address these issues, our laboratory has constructed testing panels with a tiered strategy utilizing screening assays that detect the most common causes and reflexing additional assays that assess less common etiologies. See Figure 1. Our testing algorithm panels include a rapid hemoglobin fraction monitoring test, a generic diagnostic hemoglobin electrophoresis profile, and more specific diagnostic evaluations for microcytic anemia, hereditary hemolytic anemia, methemoglobinemia and sufhemoglobinemia and erythrocytosis. Use of these testing strategies has facilitated the identification of rare and complex hemoglobin disorders from a wide variety of ethnic groups, including over 500 distinct named alpha, beta and gamma variants (of which 60+ were novel variants at the time of first detection), 99 beta thalassemia mutations and greater than 20 large deletional beta globin cluster deletion subtypes.

Introduction

Hemoglobinopathy evaluation is undertaken in a wide range of clinical situations which include newborn, prenatal or preconception screening, diagnostic testing to explain specific clinical signs and symptoms, and monitoring of hemoglobin (Hb) fractions after therapy. This varied range of test indications complicates a uniform streamlined approach to hemoglobin testing. Cost effective resource utilization requires knowledgeable application of the varied methods available and their complementary strengths and limitations to select tests best suited to answer the clinical need. In the tertiary reference laboratory setting, understanding the goal of the ordering provider and therefore the optimal extent of testing is challenging. Accurately relating the particular clinical question helps laboratorians process samples appropriately but this simple and basic information is too often not adequately communicated in real testing situations. Because the indications for hemoglobin testing are so wide-ranging, our laboratory approaches hemoglobinopathy testing in a tiered approach. See Figure 2.

Methods and Discussion

The least complex clinical situation encountered in hemoglobin testing is the monitoring of a previously confirmed hemoglobin disorder. Monitoring is frequently used in sickle cell disorder patients with recent transfusion or hydroxyurea therapy to quantify Hb A, Hb F and the abnormal variant(s). This can be rapidly accomplished using a single detection method that reliably quantitates the variant percentage. We use high performance liquid chromatography (HPLC) or capillary electrophoresis (CE) for this purpose.

The next level of complexity is a diagnostic generic hemoglobin evaluation. This is a test that carries the most ambiguity regarding the level of testing required to answer a clinical question. It is designed as a diagnostic test which detects all of the most common Hb variants, quantitates Hb A_2 for the diagnosis of beta thalassemia minor and guides further testing for uncommon hemoglobin disorders. This heavily relies upon adequate communication from referring providers for proper interpretation and utilization management. Communication can be a written information sheet or electronic comment field to relay complete blood count (CBC) values, test indication/clinical suspicion, clinical/family history, ethnicity, and data regarding recent therapeutic confounders such as transfusion or hydroxyurea administration. Our laboratory utilizes HPLC [1] and CE [2] simultaneously as screening methods. If normal tracings are obtained and no further indication is known to be present, the result is released as negative with a caution statement that addresses the types of conditions that further evaluation could be considered. If indicated, additional tests are performed according to the possible identification of the disorder suspected. These can include sickle solubility, isoelectric focusing, hemoglobin stability (heat and isopropanol), flow cytometry for Hb F red cell distribution, mass spectrometry (MS) and molecular studies to include DNA sequencing of the alpha, beta and gamma globin genes and MLPA analysis of alpha and beta globin cluster loci. Because many methods are available, judicious use of the testing options requires clinical information and knowledge of the strengths and limitations of the methods available for diagnosis.

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To aid in the diagnosis of very complex hemoglobin disorders, a more comprehensive testing profile is offered in which HPLC and CE results are correlated with ferritin levels, possible deletional alpha thalassemia testing, and red blood cell (RBC) indices. This allows for incorporating iron deficiency and alpha thalassemia status and assumes an indication for more extensive investigations to explain the phenotype. Multifactorial causes are addressed, such as beta thalassemia trait that shows a more severe phenotype than expected, or complex Hb E disorders. This strategy has identified many electrophoretically silent clinically significant variants (Hb Adana, Hb Bronovo, Hb Taybe) that may be missed by our routine hemoglobin electrophoresis test offering.

Some indications for hemoglobin testing encompass a broader scope of RBC disorders. To address these needs we use panels focused on particular signs and symptoms, in particular, hemolysis, methemoglobinemia, or erythrocytosis. The panel that assays for hereditary causes of hemolysis includes hemoglobin (with frontline stability study testing), RBC enzyme and membrane disorder testing. It incorporates RBC enzyme activities and osmotic fragility/EMA binding assays for membrane disorders correlated with a review of the peripheral blood smear. The addition of the stability study screen identifies many electrophoretically silent unstable Hb variants. Another panel that focuses on methemoglobinemia and sulfhemoglobinemia performs HPLC and CE, methemoglobin and sulfhemoglobin levels and methemoglobin reductase (METR) [cytochrome b5 reductase 3] activity levels [3]. This provides for the identification of M-hemoglobin variants which were historically challenging to identify using previous methods but have characteristic patterns using the HPLC method. Elevated methemoglobin or sulfhemoglobin values prompt further investigation for a variant that can be subtle or silent by electrophoresis and HPLC, such as Hb Volga. In addition, this profile also assesses for METR deficiency-associated congenital methemoglobinemia.

Our laboratory has found great utility in a panel for the evaluation of hereditary erythrocytosis which includes frontline oxygen dissociation curve (p50) and MS testing [4]. Serum erythropoietin and p50 results efficiently guide reflex testing from the 19 different assays available for erythrocytosis. In our experience, hereditary erythrocytosis is commonly caused by high oxygen affinity hemoglobin variants (HOA) which are associated with a decreased p50 value. Many HOAs have neutral charge substitutions, do not separate from Hb A using multiple protein screening methods and can result in false negative cases. Simultaneously performing MS, HPLC and CE methods allows for the detection of all of the 79 distinct alpha and beta globin chain HOA variants we have seen in our laboratory (manuscript submitted for publication). In addition, the MS method enables an estimate of variant percentages in many cases that do not separate from Hb A by other methods. When a HOA is excluded, this panel tests for erythropoietin receptor (EPOR), 2,3-bisphosphogycerate mutase (BPGM) and oxygen sensing pathway mutations (HIF2A, PHD2 and VHL) as possible etiologies for the elevated hematocrit in an algorithmic fashion.

Conclusions

In summary, indications for the evaluation of hemoglobin disorders vary from the simple to the very complex. Laboratories at tertiary reference centers harbor extensive experience but suffer from a dearth of preanalytical information critical in the accurate interpretation and efficient triaging of appropriate testing for these disorders. Creating specific testing panels based on signs and symptoms allows assignment of implied indications for testing and utilize appropriate algorithms. These testing strategies allow efficient diagnoses of rare clinically significant hemoglobin disorders and decrease widespread indiscriminate testing that wastes resources. While continued suboptimal communication between clinical caregivers and laboratorians still result in missed opportu-

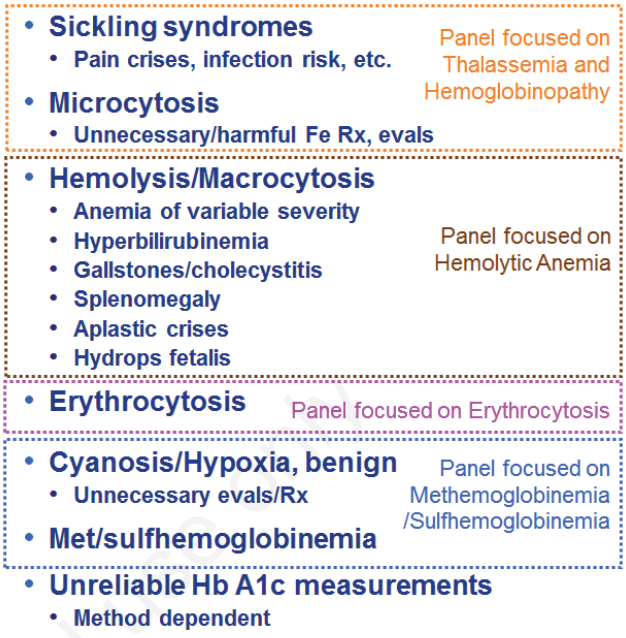

Figure 1. Hemoglobin disorders should be considered in settings other than sickling syndromes or microcytic anemia. Because hemoglobin testing includes a wide range of clinical indications ranging from monitoring of known variants, to low suspicion prenatal screening to high suspicion complex disorders, adequate communication of preanalytical data is crucial for proper and efficient testing of specimens. Creating specific assay panels based on signs and symptoms allows appropriate test utilization guided by useful algorithms.

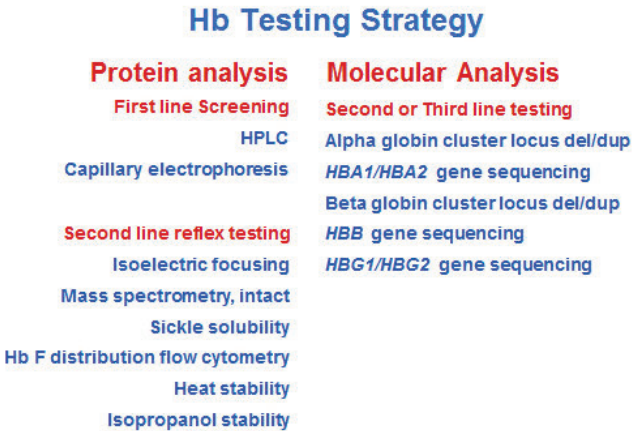

Figure 2. Hemoglobin testing strategy in a high throughput testing laboratory in the United States of America. To increase sensitivity, two screening methods are used for all diagnostic assays. Dependent upon the choice of testing ordered, additional methods may be used a frontline screening methods, such as stability studies for hemolysis, p50 assay for erythrocytosis and methemoglobin and sulfhemoglobin levels for cyanosis. An assay for monitoring previously confirmed hemoglobin disorders may use a single test that reliably separates and quantitates common hemoglobin fractions.

nities to identify all clinically significant variants, the use of these testing strategies in our laboratory has facilitated the identification of rare and complex hemoglobin disorders from a wide variety of ethnic groups, including over 500 distinct named alpha, beta and gamma variants (of which 60+ were novel variants at the time of first detection), 99 beta thalassemia mutations and greater than 20 large deletional beta globin cluster deletion subtypes [4-10].

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Optimal blood transfusion therapy in haemoglobinopathies

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For reasons of time, this short talk will be confined to the optimal frequency, timing, indications and dosing of blood transfusion. Blood transfusion protocols in thalassaemia syndromes are more widely agreed (1) than for sickle disorders but questions still remain about optimal Hb levels, timing and frequency. In transfusion thalassaemia thalassaemias (TDT) , the purpose of blood transfusion is to maximise quality of life by correcting anaemia and suppressing ineffective erythropoiesis, whilst minimising the complications of the transfusion itself. Under-transfusion will limit growth and physical activity while increasing intramedullary and extra-medullary erythroid expansion. Over transfusion may cause unnecessary iron loading and increased risk of extra-hepatic iron deposition however. Although guidelines imply a 'one size fits all' approach to transfusion, in reality this is not be the case. Indeed a flexible approach crafted to the patient's individual requirements and to the local availability of safe blood products is needed for optimal outcomes. For example in HbEβ thalassaemias, the right shifted oxygen dissociation curve tends to lead to better oxygen delivery per gram of Hb than in β thalassaemia intermedia with high Hb F. Patients with Eβthal therefore tend to tolerate lower Hb values than β thalassaemia intermedia. Guidelines aim to balance the benefits of oxygenation and suppression of extra-medullary expansion with those of excessive iron accumulation from over-transfusion. In an Italian TDT population, this balance was optimised with pre-transfusion values of 9.5-10.5g/dl (2). However this may not be universally optimal because of different levels of endogenous erythropoiesis with different genotypes in different populations. Recent work by our group (3) suggests that patients with higher levels of endogenous erythropoiesis, marked by higher levels of soluble transferrin receptors, at significantly lower risk of cardiac iron deposition than in those where endogenous erythropoiesis is less active, as would be the case in transfusion regimes achieving higher levels of pre-transfusion Hb.

In sickle cell disorders, the variability in the phenotype between patients and also within a single patient at any given time means that the need for transfusion also varies. A consideration in sickle disorders, not usually applicable to thalassaemia syndromes, is that of exchange transfusion *versus* simple top up transfusion. Exchanges have the advantages of lower iron loading rates and more rapid lowering of HbS%. Disadvantages of exchange transfusion are of increased exposure to blood products with inherent increased risk of allo-immunisation or infection, requirement for better venous access for adequate blood flow, and requirements for team of operators capable of performing either manual or automated apheresis, often at short notice. Some indications for transfusion in sickle disorders are backed up by randomised controlled data, such as for primary and secondary stroke prevention, or prophylaxis of sickle related complications for high-risk operations (4). Others are widely practiced as standard of care without randomised data, such as treatment of acute sickle chest syndrome. Other indications for transfusion, not backed up by randomised studies, but still widely practiced in selected cases, include the management of pregnancy, leg ulceration or priapism and repeaed vaso-occlusive crises. Allo-immunisation is more common in sickle patients than in thalassaemia disorders and hyper-haemolysis is a rare but growing serious problem in sickle disorders. It is arguable that increased use of transfusion early in life, is indicated to decrease silent stroke rates and that early exposure to blood will decease red cell allo-immunisation rates.

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Iron overload and chelation therapy in hemoglobinopathies

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Abstract

Iron overload (IOL) is highly prevalent among patients with hemoglobinopathies; both transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT). Whether IOL is secondary to regular transfusions like in TDT, or develops from increased intestinal absorption like in NTDT, it can cause significant morbidity and mortality. In TDT patients, iron accumulation in organ tissues is highly evident, and leads to organ toxicity and dysfunction. IOL in NTDT patients is cumulative with advancing age, and concern with secondary morbidity starts beyond the age of 10 years, as shown by the OPTIMAL CARE study. Several modalities are available for the diagnosis and monitoring of IOL. Serum ferritin (SF) assessment is widely available and heavily relied on in resource-poor countries. Non-invasive iron monitoring using MRI has become the gold standard to diagnose IOL. Three iron chelators are currently available for the treatment of IOL: deferoxamine (DFO) in subcutaneous or intravenous injection, oral deferiprone (DFP) in tablet or solution form, and oral deferasirox (DFX) in dispersible tablet (DT) and film-coated tablet (FCT). Today, the goal of ICT is to maintain safe levels of body iron at all times. Appropriate tailoring ICT with chelator choices and dose adjustment must be implemented in a timely manner. Clinical decision to initiate, adjust and stop ICT is based on SF, MRI-LIC and cardiac T2*. In this article, we review the mechanism of IOL in both TDT and NTDT, the pathophysiology behind it, its complications, and the different ways to assess and quantify it. We will also discuss the different ICT modalities available, and the emergence of novel therapies.

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Introduction

Thalassemia is an inherited disease with multiple genetic forms, including alpha-thalassemia, beta-thalassemia, hemoglobin E/beta thalassemia, and others. Molecular defects in the alpha-globin gene cluster on chromosome 16 or the beta-globin gene cluster on chromosome 11 result in defective hemoglobin synthesis. This in turn leads to an imbalance in the relative quantity of alpha-globin and beta-globin chains [1]. Therefore, the disease hallmarks consist first and foremost of the before mentioned imbalance in the α/β-globin chain ratio, which in turn leads to the following cascade of events and disease hallmarks including ineffective erythropoiesis, and chronic hemolytic anemia (Figure 1).

Thalassemic disorders lie on a spectrum of severity with different clinical phenotypes, complications, and strategies for treatment. The grade of this severity relies on the significance of the globin gene mutation and coinheritance of other genetic determinants. [2] The degree of transfusion dependence is one of the elements considered in a recent classification of thalassemic disorders into transfusion- dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT). Iron overload (IOL) is highly prevalent among patients with hemoglobinopathies. Whether IOL is secondary to regular transfusions like in TDT, or develops from increased intestinal absorption like in NTDT, it can cause significant morbidity and mortality. In TDT patients, iron accumulation in organ tissues is highly evident, and leads to organ toxicity and dysfunction. In NTDT patients, IOL is cumulative with advancing age, and concern with secondary morbidity starts beyond the age of 10 years. [1] In this article, we review the mechanism of IOL in both TDT and NTDT, the pathophysiology behind it, its complications, and the different ways to assess and quantify it. We will also be addressing the different ICT modalities available, and discuss the emergence of novel therapies targeting IOL.

Mechanism of iron overload in transfusion dependent thalassemia and non-transfusion dependent thalassemia

The predominant mechanisms driving the process of iron loading include increased iron burden secondary to transfusion therapy in TDT and enhanced intestinal absorption secondary to ineffective erythropoiesis and hepcidin suppression in NTDT. Different organs are affected differently by iron overload in TDT and NTDT owing to the underlying iron loading mechanism and rate of iron accumulation[1].

Unfortunately, the human body lacks a physiological mechanism for removal of the excess iron load resulting from blood transfusion[3]. Each unit of transfused packed red blood cells contains 200 to 250 mg elemental iron. In TDT, transfusional iron usually amounts to 0.3 to 0.6 mg/kg per day with an assumed monthly transfusion rate of 2 to 4 U packed red blood cells. Senescent transfused red blood cells are phagocytized by the reticuloendothelial macrophages. This leads to the release of cellular iron into the

plasma to bind transferring; which is the main iron transport protein and is capable of binding two Fe^{3+} Molecules at once. It is only when transferrin binding gets saturated, that we start having iron accumulation: because the now non-transferrin-bound iron (NTBI) is readily transported through calcium channels into the liver (hepatocytes), heart (cardiac myocytes), and endocrine glands. The accumulation of iron in different organs leads to the different clinical complications of IOL [1, 3]. This accumulation of NTBI in different types of cells leads to its metabolism and the production of reactive oxygen species (ROS) contributing to the cellular dysfunction, apoptosis, and necrosis seen in the target organs[3, 4].

Transferrin carrying 2 molecules of Fe^{3+} then binds to transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2), then gets endocytosed. The acidic environment of the lysosomes, causes the release of Fe^{3+} from transferrin, and its reduction to Fe^{2+}. Fe^{2+}then reaches the cytosol through divalent metallic transporter 1[1]. While TfR2 is uniquely expressed in the liver and intestine, TfR1 is expressed in most tissues, including erythroid precursors, the liver, and the myocardium. The affinity of TfR1 for iron is higher than that of TfR2 by ~25 times. Interestingly, TfR2 lacks an iron responsive element, and iron loading continues to happen in the liver despite high liver iron concentration (LIC), while TfR1 is downregulated with elevated transferrin saturation. Previously, the most important clinical complication of iron overload has been cardiac siderosis, which is at the origin of arrhythmias and heart failure and has been a major cause of mortality in TDT. However, with the advances in IOL diagnosis and management nowadays, cardiac mortality has declined significantly, allowing light to be shed on hepatic and endocrine dysfunction as other complications of IOL in TDT patients[4].

Even in the absence of regular red blood cells transfusions, IOL still develops in patients with NTDT. Remarkably, it has been noted that iron accumulation preferentially occurs in the liver in patients with NTDT and rather than the myocardium. This was established after observational studies showed absence of cardiac siderosis even in patients with severely elevated liver iron content (LIC) [5]. Normally, Hepcidin synthesis by the liver suppresses the release of iron from erythroid precursors, hepatocytes, basolateral membranes of hepatocytes, and macrophages by binding to ferroportin, which mediates iron export[1]. It is believed that the ineffective erythropoiesis, along with the state of chronic anemia/hypoxia leads to the inappropriately low levels of hepcidin. This in turn contributes to IOL through two mechanisms: increased intestinal iron absorption through lowering ferroportin, and increased release of recycled iron from the reticuloendothelial system. This in turn leads to preferential portal and subsequently hepatocyte iron loading, depletion of macrophage iron, and relatively lower levels of serum ferritin (compared to TDT patients) [6].

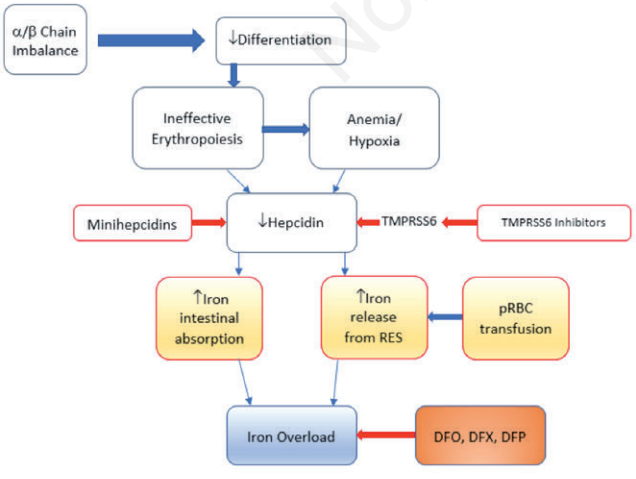


Figure 1. Pathophysiology, mechanism of IOL and novel therapies targeting IOL in β-Thalassemia. TMPRSS6, transmembrane protease serine 6; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Iron overload complications in transfusion dependent thalassemia and non-transfusion dependent thalassemia

Iron overload complications in transfusion dependent thalassemia

As previously mentioned, when iron content surpasses transferrin binding capacity and hemosiderin/ferritin storage ability, toxic NTBI enters mitochondria and leads to the formation of toxic radicals and ROS. This in turn leads to gene alterations resulting in cell apoptosis and or fibrosis in different target organs including the myocardium, liver, and endocrine glands [7]. Given the constant need for blood transfusions in TDT, along with hypoxia/anemia induced hepcidin suppression, IOL occurs at a faster rate in TDT patients when compared to NTDT patients. This is also evident in the clinical course of the two diseases, as IOL complications are more pronounced in the TDT group.

a. Cardiac complications – Despite the advances in ICT, cardiovascular disorders remain the leading cause of morbidity in TDT patients, and it remains crucially important for clinicians to recognize it early on as it mandates intensified chelation therapy. IOL related cardiac complications include reversible myocyte injury, arrhythmias including heart block, and arterial changes with loss of vascular compliance [7-9].
b. Hepatic complications – The liver is another organ that is highly susceptible to IOL induced damage in TDT patients. Hepatic macrophages known as Kupffer cells are primarily affected due to their role in RBC degradation. The intra-macrophagic iron will be released in the bloodstream in a progressive manner. During this process, plasma transferrin gets saturated which leads to the appearance of NTBI. NTBI will in turn target different organs including the heart, liver and endocrine organs. Hence controlling liver iron content is crucial to protect the liver along with the other organ systems [10]. Hepatic complications comprise hepatic fibrosis, cirrhosis, and in cases hepatocellular carcinoma [11].
c. Endocrine and bone complications – Endocrine disorders seen in TDT patients due to IOL include short stature and growth retardation, hypogonadism and delayed puberty, hypothyroidism, impaired glucose tolerance and diabetes mellitus, hypoparathyroidism, adrenal insufficiency as well as osteoporosis [12, 13].

Iron overload complications in non-transfusion dependent thalassemia

NTDT is associated with a high morbidity profile that can start manifesting as early as 10 years of age. Iron burden and accumulation stands behind some of the complications seen in NTDT: by promoting oxidative damage in different organs of the body, and inducing multiple organ dysfunction.

a. Cardiac Disease – Whereas cardiac disease is one of the most important causes of morbidity/mortality in patients with TDT,

it is manifested in a less severe manner in patients with NTDT. In fact, while IOL in TDT leads to left ventricular (LV) dysfunction, heart failure and in severe cases to cardiogenic shock, cardiac complications in NTDT are related to right sided heart failure secondary to pulmonary hypertension [8]. However, the risk of LV decompensation in patients with NTDT is minimal, but increases with age. This might be explained by the fact that iron deposition in the myocardium happens at a faster rate and is much more common in patients with TDT when compared to patients with NTDT [14]. Moreover, when compared to healthy individuals, patients with NTDT were found to have a higher prevalence of rhythm disorders, pericardial diseases and valvular abnormalities [8, 9].

b. Liver Complications – In NTDT, most iron accumulation targets the liver, and patients are at an increased risk of hepatic fibrosis, cirrhosis, and eventually developing hepatocellular carcinoma (HCC). IOL is one of the most important risk factors for hepatic failure and cirrhosis seen in thalassemia patients. Even in the absence of chronic hepatitis C (HCV) infection, NTDT patients are at an increased risk of HCC due to IOL. As already mentioned, iron accumulation is associated with the formation of free radicals and reactive oxygen species (ROS) in different target organs, specifically hepatocytes leading to cellular damage by inflicting damage to tumor suppressor genes and DNA repair genes. Moreover, iron has a profibrogenic effect which in turn accelerates the development of liver cirrhosis [15, 16].
c. Endocrinopathies – Iron accumulation can also disrupt the hypothalamic-pituitary axis (HPA), leading to an array of endocrine diseases in thalassemia patients such as hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus, and adrenal insufficiency. Endocrinopathies form an important source of morbidity in NTDT patients, but with a lower prevalence than their counterparts in TDT. This may be attributed to the hepatic dominance of iron loading and to the slower rate at which IOL occurs in patients with NTDT [17, 18].
d. Kidney disease – Kidneys are also affected by iron overload, manifesting as proteinuria, and glomerular hyperfiltration as a result of glomerular and tubulointerstitial injury. It is important to mention that damage to the glomerulus and the tubulointerstitial systems are not only caused by IOL; the chronic state of anemia and hypoxia play a crucial in this too. End stage kidney disease is a possible outcome of IOL induced renal damage in patients with NTDT [19, 20].
e. Bone Disease – Iron overload, splenectomy, low fetal hemoglobin levels and female gender appear to be associated with a higher risk of osteoporosis in NTDT patients [21-23]. On the other hand, ICT and hydroxyurea use were correlated with lower rates of osteoporosis.

Diagnosis and Quantification of iron overload in transfusion dependent thalassemia and non-transfusion dependent thalassemia

Magnetic resonance imaging

Given its safety and reliability when compared to the invasive liver biopsy, MRI using T2* (in milliseconds) and R2* imaging techniques are now considered the gold standard for LIC quantification. T2* relaxation refers to decay of transverse magnetization caused by a combination of spin-spin relaxation and magnetic field inhomogeneity[24]. This relaxation occurs faster (shorter T2* in ms) with increasing tissue (myocardial, liver…) iron concentrations [1, 24].

Moreover, Angelucci et.al demonstrated that LIC estimated from MRI imaging in mg of iron per gram of liver dw correlates reliably with total body iron stores [10]. Most guidelines now rely on LIC and T2* from MRI to diagnose IOL and adapt ICT [1]. Specific LIC and cardiac T2* thresholds have been associated with morbidity in TDT and NTDT [11, 25]:

- In NTDT, LIC values greater than 5 mg/g dw were associated with increased morbidity.
- In TDT, LIC values greater than 7 mg/g dw are used to indicate increased risk for complications related to iron overload, while LIC values >15 mg/g were predictive of advanced liver fibrosis, mortality, and increased risk of cardiac disease in TDT [10, 25].
- Cardiac T2* values lower than 10 ms is highly associated with increased risk of symptomatic heart failure and higher mortality in TDT [26].
- Cardiac T2* values between 10 and 20 ms were associated with lower left ventricular ejection fraction (LVEF) and a higher risk of arrhythmias in TDT [26].

Serum ferritin assessment

The unavailability of MRI in the developing countries where Thalassemia is most prevalent (Sub-Saharan Africa, Middle East, India, Mediterranean region, and Southeast Asia), and its high cost form major limitations to its use as a tool to quantify and guide ICT. Therefore, the assessment of serum ferritin values and their correlation with LIC becomes of crucial value. In NTDT for example, cutoffs of 300 ng/mL and 800 ng/mL were identified: whereas SF levels lower than 300 ng/mL indicate absent IOL and SF levels higher than 800 ng/mL indicate significant IOL [27]. Moreover, results from the ORIENT study revealed that patients with SF ≥800 µg/L have a higher incidence of morbidities over 11 years. Based on a ROC analysis, a SF level of ≥800 µg/L had the highest accuracy for predicting LIC ≥5 mg Fe/g dw. As for the SF values between 300 and 800, a recent evaluation found that a significant proportion of those NTDT patients had IOL requiring treatment [28]. As for TDT, the cutoff used to initiate ICT is 1000 ng/mL since SF levels lower than 1000 ng/mL were associated with lower morbidity and mortality in TDT and this threshold is most commonly use to indicate the need for initiation and as a target for [4, 29]. In a multicenter study conducted in 2017 by Krtittayaphong *et al.* SF levels had limited ability to correlate with cardiac iron overload in TDT, but were found to predict cardiac siderosis when values were greater than 2500 ng/mL [30].

SQUID

LIC can also be derived from the paramagnetism in the liver. This can be measured using superconducting quantum interference device known as SQUID [31]. However, three major drawbacks made SQUID a rarely used technique for LIC measurement: it is costly since it utilizes liquid helium, the apparatus needs to be away from all paramagnetic forces (cars, lifts…) making it impractical, finally it relies on strong mathematical methods and different calibration methods between different devices making the comparison of results between different devices trickier [31].

Iron chelation therapy

Iron chelation therapy (ICT) is and will always remain the standard method of choice in thalassemia management, decreasing morbidity and mortality in this patient population. The primary goal of ICT today has shifted from treating or rescuing IOL to maintaining safe levels of body iron at all times [32]. Moreover, appropriate tailoring ICT with chelator choices and dose adjust-

ment must be implemented in a timely manner. The clinical decision to initiate, adjust and stop ICT is based on SF, MRI-LIC and cardiac T2*. Three iron chelators are currently available for the treatment of IOL: deferoxamine (DFO) in subcutaneous or intravenous injection; oral deferiprone (DFP) in tablet or solution form; and oral deferasirox (DFX), in dispersible tablet (DT) and—more recently—film-coated tablet (FCT) forms [32-34] (Table 1).

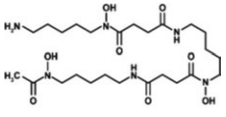
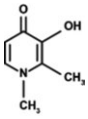
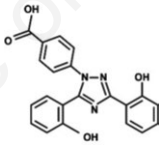
Iron chelation therapy in transfusion dependent thalassemia

In TDT patients, choices of ICT monotherapy may vary. As first line of treatment the following is recommended: DFO 30-60 mg/kg/day, administered over a span of 8–10 hours a day, 5–7 days a week; or DFX 20-40 mg/kg/day administered once daily [32]. For second line treatment, and when ICT with DFX or DFO is inadequate, DFP is given at a dose of 75-100 mg/kg/day divided over three doses [32]. Possible combination therapies that have been recommended include DFO+DFP, DFO+DFX and DFP+DFX [35-37]. Indications to intensify ICT in TDT: SF ≥2500 ng/mL and/or LIC >7 mg/g dry wt. liver and/or cardiac T2* <20 msec. In TDT patients, the indication to stop ICT: SF <300 ng/mL and/or LIC <3 mg/g dry wt. liver [32] (Table 2).

a. Approach to myocardial IOL – The risk of cardiac dysfunction increases with increasing levels of myocardial iron. High myocardial iron is strongly associated with heart failure and death. Myocardial clearance with ICT occurs at the same time as liver clearance, but is slower in the heart than in the liver. Most prospective studies looking at the efficacy of iron chelators in myocardial iron removal are DFX studies. DFX is the only chelator to have demonstrated efficacy in removing myocardial iron in patients with high baseline LIC.

   Results from a 1-year prospective randomized comparison of DFO+DFP combination therapy *vs* DFO monotherapy conducted on TDT patients with mild to moderate myocardial IOL

Table 1. Characteristics of the currently available iron chelators in thalassemia management [2, 77].

	DFO	DFP	DFX
Structure			
Administration route Administration time	Subcutaneous orIntravenous Every 8-12 hours5-7 days/week	Oral (tablets or solution) 3 times daily	Oral (dispersible tablet or film-coated tablet) Once daily
Half-life Recommended dose	20-30 minutes 30-60 mg/kg/day	3-4 hours 75-100 mg/kg/day	12-16 hours TDT: 20-40 mg/kg/dayNTDT: 5-20 mg/kg/day
Route of iron excretion Adverse Events	Urinary and fecal Delay in bone growth, auditory and ocular complications, local reactions and allergies	Urinary Gastrointestinal complications, Neutropenia/agranulocytosis, arthralgia, elevated hepatic enzymes	Fecal Gastrointestinal bleeding ulceration, and irritation, elevated hepatic enzymes, increased creatinine, liver failure and renal insufficiency, skin rashes

TDT, Transfusion-dependent thalassemia; NTDT, non-transfusion-dependent thalassemia; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Table 2. Iron overload characteristics and iron chelation therapy indications in transfusion dependent thalassemia *vs* non-transfusion dependent thalassemia [78].

	TDT	NTDT
Mechanism of IOL	Blood transfusion	Increased intestinal absorption
Rate of iron accumulation	Fast	Slow
IOL-related complications	Cardiac siderosis, heart failure and cardiac arrhythmia, liver fibrosis and cirrhosis, endocrinopathies	Liver fibrosis, cirrhosis and HCC, endocrinopathies, proteinuria and glomerular hyperfiltration, thrombosis, PHT, osteoporosis, osteopenia
Indication to initiate ICT	SF ≥1000 ng/mL orLIC ≥3 mg/g dry weight liver	SF ≥800 ng/mL and/orLIC ≥5 mg/g dry weight liver
Indication to intensify ICT	SF ≥2500 ng/mL and/or LIC >7 mg/g dry wt. liver and/or Cardiac T2* <20 msec.	LIC after 6 months of treatment >7 mg/g dry wt. liver or SF >1500-2000 ng/mL
Indication to stop ICT	SF <300 ng/mL and/or LIC <3 mg/g dry wt. liver	SF <300 ng/mL and/or LIC <3 mg/g dry wt. liver
Choices of ICT-Monotherapy	DFO 30-60 mg/kg/day DFX 20-40 mg/kg/day DFP 75-100 mg/kg/day	DFX 5-20 mg/kg/day
Choices of ICT-Combination Therapy	DFO+DFP DFO+DFX DFP+DFX	N/A

TDT, transfusion-dependent thalassemia; NTDT, non-transfusion dependent thalassemia; SF, serum ferritin; LIC, liver iron concentration; HCC, hepatocellular carcinoma; PHT, pulmonary hypertension; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

(T2* 8–20 ms) showed that at 12 months, myocardial T2* improved significantly in both groups [38]. However, the between-group difference was significantly in favor of combination therapy. In comparison with the standard IOL using DFO, combination therapy with DFP showed greater reduction in myocardial iron and improved LVEF [38] . Therefore, combination therapy should be considered in patients whose DFO monotherapy fails to achieve adequate control of myocardial iron [38]. However, addition of DFP to DFO did not always enhance myocardial iron removal in patients with severe myocardial IOL. The cardiac sub study of the EPIC trial, a 1-year, multicenter, prospective longitudinal study, looked at the effect of DFX in removing cardiac iron in patients with β-thalassaemia and myocardial siderosis over 3 years and showed that DFX continually improved myocardial T2* across 3 years irrespective of baseline myocardial iron severity [39]. Different chelators have different strengths in removing NTBI and lowering mitochondrial oxidative stress. Nevertheless, DFX and DFP both improve endothelial function over time [7].

b. Approach to hepatic IOL – With increasing LIC, liver enzymes increase, as well as liver fibrosis. Organ damage and dysfunction can progress [40]. LIC is the best measure of total body iron stores and helps to predict the risk of hepatic and extrahepatic complications [41, 42]. Effective ICT reduces LIC and may prevent progression of liver disease. LIC levels >7 mg/g dw are associated with increased risk of morbidity and liver disease. LIC levels >15 mg/g dw are associated with increased aminotransferase enzymes concentration, increased risk of hepatic fibrosis and hepatocellular carcinoma (HCC), increased risk of HCC secondary to cirrhosis and increased risk of cardiac disease [40, 42, 43]. DFO therapy has been shown to be associated with a significant decrease in LIC in patients TDT. DFX has also been shown to significantly decrease LIC by 3.1 to 7.8 mg/g dw in patients with TDT [44]. One study showed that DFX doses >30 mg/kg per day were needed to achieve optimal improvement in LIC in patients with heavy IOL in TDT [45]. DFX monotherapy and DFP monotherapy have been shown to improve hepatic siderosis [35, 46, 47] However, there is no head-to-head trial comparing DFX and DFP at optimal doses. Based on the most robust data available, we recommend monotherapy with DFX, at a dosage of 20 to 30 mg/ kg or higher per day, or combination therapy with DFO and DFX for the treatment of hepatic siderosis in TDT [37, 44, 48].I n patients with high LIC, combination therapy of DFX+DFO has been shown to significantly reduce LIC.

c. Approach to IOL in the endocrine organs – Endocrinopathies still account for significant morbidity in TDT [12, 49-51]. For example, pancreatic iron loading (defined as MRI R2* >100Hz) and severe pituitary iron deposition may possibly develop during the first decade of life [52, 53]. Intensive combination therapy of DFO and DFP has been associated with prevention and/or reversal of endocrine complications in general [54]. Combined DFP/DFX treatment has also been shown to prevent or reverse endocrine complications in TDT patients. In a recent multicenter retrospective cohort study by Casale *et al.*, the low prevalence of new endocrine disorders and stabilization of preexisting ones during DFX therapy, suggest that DFX may play a protective in endocrinopathies [55].

Iron chelation therapy in non-transfusion dependent thalassemia

While all three iron chelators have proven their effectiveness as iron chelators in TDT patients, DFX remains the only drug that has received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for use in NTDT patients, mostly based on results extracted and published from the THALASSA trial [56, 57]. In this multinational, prospective, randomized, double-blinded phase II trial 1-year DFX treatment of NTDT patients >10 years was found to decrease LIC at a daily dose of 5 and 10 mg/kg, respectively, compared to placebo [57]. Sub-analyses further proved DFX 5 and 10 mg/kg/day starting doses led to consistent reductions in LIC across all patients, irrespective of baseline LIC, SF, underlying NTDT form, splenectomy status or demographics such as age, gender and race [57]. The analyses also showed that greater reductions in LIC were achieved in patients dose-escalated at 6 months from DFX 10 mg/kg/day starting dose to 20 mg/kg/day [57]. A 1-year extension phase was then carried out to allow for the assessment of up to 2 years of DFX treatment. Patients continued to respond, with a decrease in LIC and SF over 2 years. Data extracted from the THETIS study [58] further showed that a starting dose of 10 mg/kg/day of DFX is effective in reducing IOL in NTDT, and that dose escalation up to 30 mg/kg/day should be considered starting at week 4 based on LIC response [58]. DFP has not been extensively studied in NTDT. Single-arm, open-label studies with small sample sizes and a more recent randomized controlled trial showed significant decreases in SF and LIC with DFP therapy [59]. DFO has not been systematically studied in NTDT, although studies with small sample sizes and short durations have shown an increase in urinary excretion of iron and a decrease in SF.

In NTDT, specific indications have been established for the initiation, dose escalation and termination of ICT. DFX chelation with initial starting dose of 10 mg/kg/day should be started in patients ≥10 years of age (15 years of age in hemoglobin H disease) if their LIC ≥5 mg Fe/g dry weight, or if their SF concentration was found to be ≥800 µg/L when LIC is not available due to lack of the necessary MRI technology [33]. As for monitoring of iron levels, LIC should be repeated 6 months after therapy initiation, with follow up every 6–12 months, in addition to SF levels being measured every 3 months [33]. If at 6 months LIC is still >7 mg Fe/g dry weight (or SF >1500 µg/L only if LIC is unavailable) with less than 15% reduction in baseline values, dose escalation should be considered up to 20 mg/kg/day [33]. DFX therapy can be safely discontinued when patients reach an LIC value of 3 mg Fe/g dry weight (or SF level of 300 µg/L only if LIC is unavailable) [33]. In NTDT, it is recommended to intensify ICT if the LIC after 6 months of treatment >7 mg/g dw. liver or SF >1500–2000 ng/mL and <15% decrease from baseline. Indications to stop ICT in NTDT include a SF <300 ng/mL and/or LIC <3 mg/g dry wt. liver (Table 2).

Adherence and advances in iron chelation therapy

Compliance with ICT is associated with effective control of IOL and improved patient survival [60, 61]. Moreover, adherence to long-term ICT is crucial in preventing IOL-related complications. For example, barriers to optimal adherence to DFX-DT include preparation time, palatability, the need to take the drug in a fasting state, and drug-related side effects, notably gastrointestinal (GI) tolerability [62]. A new FCT formulation was developed, which is swallowed once-daily, whole or crushed, with or without a light meal [62]. The open-label, phase II ECLIPSE study evaluated the overall safety, as measured by the frequency and severity of adverse events (AEs) and changes in laboratory values, in patients treated with DFX-FCT or DFX- DT. Overall incidence of AEs was similar between treatments, but there were fewer serious adverse events (SAEs) with FCT. The study also evaluated patient-reported outcomes (PRO) in TDT or lower-risk myelodysplastic

syndromes patients randomized to receive DFX DT or FCT over a 24-week period [62]. FCT recipients consistently reported better adherence, greater satisfaction, and fewer concerns, with a safety profile consistent with the known DT formulation. These findings suggest a preference in favor of the new formulation, with better patient satisfaction and adherence translating into reduced IOL-related complications.

Iron chelation therapy in special populations: Pediatric population

Pediatric TDT patients require adequate blood transfusions for normal growth and skeletal development. The goals of blood transfusion therapy in children with TDT include correction of anemia, suppression of erythroid expansion and bone changes, prevention of spleen enlargement and hypersplenism and ensure appropriate growth and development. TDT patients may have liver IOL as young as age 2 years. Young TDT patients may also have myocardial IOL [63]. Guidelines for pediatric patients include maintaining an average Hb of 12 g/dL, max 14 g/dL, a pre-transfusion Hb of 9–10.5 g/dL, and transfusing pRBC units only: starting with low transfusion frequency in young patients and increase as they grow. Chelation strategies initiated timely and adjusted appropriately in children must be warranted to prevent permanent organ damage that might lead to significant morbidity later in life [64]. DFO has been shown to reduce serum ferritin in children with IOL [64]. However, high DFO doses in pediatric patients with low serum ferritin may result in growth failure, which should be distinguished from growth retardation secondary to inadequate transfusion or IOL [65]. In such cases, close monitoring of growth rate, DFO dose/regimen is recommended. Dose reduction was also found to restore growth rate to pre-treatment levels in some cases. Therefore, it is recommended to check on body weight and height every 3 months in children [32]. The experience in DFP is the most limited, with studies available showing it may not be as effective to reduce iron in young children [66]. DFX therapy has been shown to have a long-term efficacy in TDT patients as young as 2 years of age, with no observed negative effects on growth or sexual development [67]. It is important to mention that challenges in the treatment of thalassemia change with age. In early childhood, the clinician must ensure adequate support and therapy to optimize growth and development. In late childhood and adolescence, sexual development and transition of care are important areas of focus. As patients transition in to adulthood, the goals of therapy include preventing long-term complications related to anemia, IOL, and hypercoagulability [68].

Novel therapies targeting iron overload

Newly emerging therapies targeting iron dysregulation include minihepcidins, and transmembrane protease serine 6 (TMPRSS6) (Figure 1).

Minihepcidins

Minihepcidins, or long-acting hepcidin analogs, have been shown to restrict iron absorption, and their utilization has shown beneficial effects on ineffective erythropoiesis and consequently IOL [69-71]. These long acting hepcidin analogs have shown to increase the levels of endogenous hepcidin, thus decreasing iron absorption from the GI tract, and increasing the redistribution of iron, thereby limiting end-organ toxicity [72]. Studies conducted on mice have also shown that minihepcidin therapy can increase Hb concentrations, and also decrease reticulocyte counts in addition to reducing spleen size [72, 73].

TMPRSS6

Several studies have been reported on the use of transmembrane protease serine 6 (TMPRSS6) as an approach to stimulate endogenous hepcidin production [74-76]. TMPRSS6, a transmembrane serine protease, acts by reducing the production of hepcidin. Thus, endogenous hepcidin production can be stimulated by reducing the expression of TMPRSS6. Through data from mouse models, it has been shown that TMPRSS6 gene deletion not only improves anaemia but also reduces ineffective erythropoiesis, splenomegaly, and IOL [74]. Other studies have shown that the use of antisense oligonucleotides or small interfering RNAs that target TMPRSS6 lead to improvements in anaemia and IOL [75, 76] Genetic ablation of TMPRSS6 also improved ineffective erythropoiesis and decreased splenomegaly in NTDT patients, without a concomitant decrease in erythropoietin production [74].

Conclusions

In conclusion, IOL represents an important clinical problem in thalassemia patients. Adequate assessment and monitoring of IOL in TDT and NTDT patients, in addition to tailored ICT, is crucial for preventing the complications known to be associated with this increased iron burden. New treatment modalities are currently being investigated to broaden options available for TDT and NTDT management, with ultimate goals of prolonging longevity, promoting greater compliance and better adherence and improving quality of life. Since both TDT and NTDT patients present with multiple pathophysiologies, tailoring treatment will always remain essential.

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Endocrine complications

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Introduction

More than five decades ago, thalassemia major (TM) was fatal in the first decade of life. This poor prognosis changed since the survival rates started to increase progressively thanks to the implementation of continuous and significant improvement of diagnostic and therapeutic methods, consisting mainly of an intensive transfusion program combined with chelation therapy and imaging methods.[1-4]

Regular red blood cell (RBC) transfusions eliminate the complications of anemia, compensatory bone marrow expansion, bone changes and splenomegaly, restore the physiological growth throughout childhood and extend survival. The most serious disadvantage of life-saving transfusions is the inexorable accumulation of iron within tissues. Iron is physiologically stored intracellularly in the form of ferritin, a protein whose synthesis is induced upon the influx of iron. When the storage capacity of ferritin is exceeded, pathological quantities of metabolically active iron are released intracellularly in the form of hemosiderin and free iron within an expanded labile pool. This metabolically active iron catalyzes the formation of free radicals, which damage membrane lipids and other macromolecules, leading to cell death and eventually organ failure. Other factors contributing to the variability of cellular iron overload are: a) the cell surface transferrin receptors and the capacity of the cells to deploy defence mechanisms against inorganic iron; b) individual susceptibility to iron toxic effect; c) the development of organ(s) damage secondary to persisting severe iron overload in the years preceding iron chelation therapy; and d) liver disorders, chronic hypoxia and associated endocrine complications.[1-3]

Multi-transfused thalassemia major (TM) patients frequently develop severe endocrine complications mainly due to iron overload, anemia, and chronic liver disease, which require prompt diagnosis, treatment and close follow-up by specialists.[4]

Hypogonadism

The most common endocrine complication documented in TM patients is hypogonadotropic hypogonadism which increases with age and the associated comorbidities.[3] The incidence rate of hypogonadism, in both sexes, varies considerably between countries and much more between specialized centers, ranging from around 50% and may even approach 100%.[1-4]

Hormone replacement therapy with sex steroids aims to relieve symptoms and signs of androgen or estrogens deficiency, using convenient and effective formulations of testosterone or estrogen/progesterone. Despite the large number of TM patients for whom HRT is prescribed, little prospective data exist to aid clinicians in making evidence-based decisions for the optimal treatment regimens. Furthermore, no evidence-based guidelines for the management of these patients exist, and many recommendations are based on theoretical knowledge about physiology and endocrinology and extrapolated from the evidence of HRT in normal postmenopausal females. Further investigations are needed to understand whether HRT should be continued until the average age of menopause. No data are available to evaluate the impact of HRT therapy in TM patients on other risk factors associated with the disease such as liver dysfunction and impaired glucose tolerance. Long-term risks for the development of breast cancer, endometrial cancer, venous thromboembolism, and cardiovascular events are not known.[5-7]

In conclusion, long-term HRT is required for relief the symptoms of hypogonadism and to prevent long-term health sequel of testosterone or estrogen deficiency. The type of HRT, dosage, and route of administration are extremely complex in patients with thalassemia because of the chronicity of treatment and because many physical and psychological changes take place during the treatment period.Therefore, international research consortia should be established to allow investigation of these important questions, and to allow clinicians to make the best possible health care HRT treatment decisions.

Glucose abnormalities in patients with thalassemia major

Glucose tolerance abnormalities and diabetes mellitus (DM) are common complications in patients with TM. Disturbances of glucose homeostasis range from increased insulin resistance and mild glucose intolerance to overt diabetes mellitus. Patients with mild disorders are usually asymptomatic; impaired glucose tolerance (IGT) is common, occurring in up to 24.1%.[8-11] Unfortunately, this represents an additional potential risk to their cardiac function.[12]

Although iron overload induced DM shares certain characteristics with both type 1 diabetes and type 2 diabetes, it appears to be a separate entity with a unique pathophysiology. As in type 1 DM, insulin deficiency is a primary defect; however, it is usually relative rather than absolute. Similar to type 2 DM, the onset of the disease is usually gradual and insidious and insulin resistance is detected in some patients.

Pancreatic iron loading in these patients begins after the first decade of life and the incidence of complications increases with age. The rate of iron accumulation is directly related to the annual blood consumption, the delay in starting chelation and to low compliance and/or inadequate chelator doses. While glucose intolerance occurs at an early stage of adolescence, DM frequently occurs

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at later stages and is usually secondary to iron overload and subsequent chronic liver disease. Depending on the age composition of cohorts, up to 25% of patients with TM may have isolated impaired fasting plasma glucose (FPG), a condition in which the fasting blood glucose is elevated above what is considered normal, but is not high enough to be classified as DM. FPG has a good correlation with other glycemic indices such as fasting insulin, insulin resistance index and beta cell function index. Impaired FPG is considered a pre-diabetic state. However, it is not known how many patients with TM with impaired FPG progress over the years to diabetes. The prevalence of DM and impaired glucose tolerance (IGT) in adolescents and young adults with TM conventionally treated with DFO varies in different series (up to 10.5% and 24%, in different series. The considerable variation in the occurrence of glycemic abnormalities can be partially explained by the marked differences in the age composition of cohorts, their genetic background, transfusion regimens, degree of chelation and the screening method used.[13-16]

Growth hormone deficiency

The diagnosis of growth hormone deficiency (GHD) is generally straightforward in children as growth retardation is present. However, in adults the diagnosis of GHD is often challenging. GHD in adults is a clinical syndrome associated with lack of positive well-being, depressed mood, feelings of social isolation, decreased energy, alterations in body composition with reduced bone and muscle mass, diminished exercise performance and cardiac capacity and altered lipid metabolism with increase in adiposity.[3]

In patients with chronic diseases, the clinical evaluation of GHD is difficult because signs and symptoms may be subtle and nonspecific, and universal provocative testing in all patients is difficult because the approach is cumbersome and expensive. Therefore, other markers are needed to identify adults who may have GHD and could potentially benefit from GH replacement therapy.[17]

Recent studies suggest that insulin-like growth factor-1 (IGF-1) may be used for primary screening, to avoid performing GH stimulation tests in the majority of healthy or diseased subjects, when appropriate normative sex and age-correlated ranges are available.[18] Therefore, the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) promoted a study to collect more information on IGF-1 values in young adult Italian thalassemia major (TM) patients. ICET-A concluded their survey with the following recommendations: A GH stimulation test should be indicated in presence of the following clinical and laboratory parameters: Short stature (Height standard deviation scores <−2.5), severe and/or prolonged iron overload, presence of severe osteoporosis and/or serum IGF-I level <−2 standard deviations. Very low IGF-1 levels, especially in those patients with childhood-onset GHD, in the presence of pituitary iron deposition and/or atrophy are highly suggestive of GHD.[19] In adult TM patients, with normal liver function, an IGF-I level <50th percentile should be taken in consideration as a cut-off level for the GH assessment.[20]

Hypothyroidism

The reported thyroid dysfunction seen in patients with TM includes primary hypothyroidism-caused abnormalities of the thyroid gland, subclinical hypothyroidism as well as secondary hypothyroidism (CH).[21-24] The frequency of hypothyroidism shows a discrepancy depending on the region, quality of management, and treatment protocols.[3,21-24] The reported frequency of thyroid dysfunctions ranges between 13% and 60% in different studies and occurs after 10 years of age regardless of difference in the rate of prevalence, largely as in the form of subclinical hypothyroidism.[21-24]

We have documented a prevalence of CH of 6% in patients with a chronological age below 21 years and 7.9% in those above 21 years.[25] Clinicians should be alert for the diagnosis of CH through accurate interpretation of thyroid function tests. We recommend L-thyroxine therapy if the level of FT4 is consistently low provided that the patient has normal cortisol levels.

Adrenal insufficiency

Accurate assessment of the hypothalamic-pituitary- adrenal (HPA) axis is essential for the management of patients with potential or suspected pituitary or hypothalamic disease that is frequent in patients with TM. [26-35] The diagnosis of AI is relatively simple when glucocorticoid secretion is profoundly depressed. [32,34] However, AI can present a difficult diagnostic challenge, especially when adrenal insufficiency is partial. This is a particularly important issue as acute crises may occur during stress periods in undiagnosed patients.[26,28,34]

Recently, several studies reported a significant prevalence of "biochemical" central adrenal insufficiency (CAI), ranging from 15% to 53.6%, [26-28] in children, adolescent and adults with TM. The pathophysiological basis of "biochemical" AI in TM has not yet been well-defined. Chronic transfusions induce iron overload in several organs, including adrenal and pituitary glands.[26,28,34] Therefore, it is possible that pituitary iron deposition might reduce ACTH secretion leading to CAI. Furthermore, the adrenal glands might also be directly affected by iron toxicity.

There are two methods to differentiate between primary and secondary AI. First is done by measuring plasma ACTH concentration in the basal fasting AM blood sample. If it is higher than normal, the patient has primary AI, whereas if it is low, the diagnosis of secondary or tertiary AI should be considered. The second method assesses the serum cortisol values in response to exogenous corticotropin (ACTH) stimulation or insulin tolerance test (ITT). The agent most commonly used is synthetic ACTH (1-24) (cosyntropin), which has the full biologic potency of native ACTH [34]. The text is useful for the diagnosis of AI but not for the differential diagnosis between peripheral and central forms. Therefore, a prolonged corticotropin administration may become helpful in the differential diagnosis. Unfortunately, this diagnostic approach has not been validated in patients with TM.[28,34]

The lack of treatment guidelines and published research often leave hematologists and internists with hesitant to approach TM patients presenting uncommon endocrine complications. Therefore, as a third step, we thought worth to prepare clinical practice recommendations for all those taking care of TM patients on current criteria for the assessment of CAI . The recommendations provide helpful information on laboratory parameters and their interpretation, as well as adrenal hormone replacement dosages and management strategies. The guidelines emphasize that clinicians need to suspect AI earlier in TM patients with risk factors, such as advanced age, severe iron overload and/or poor compliance to therapy, and with multiple endocrine complications.

Hypoparathyroidism

In the general population, hypoparathyroidism (HPT) can be transient or permanent, inherited or acquired, or caused by inabili-

ty of parathyroid gland to synthesize or secrete PTH. This may be due to abnormal development of the parathyroid gland, destruction of parathyroid tissue, or peripheral resistance to PTH.

It is a rare disease, with the leading clinical symptoms of hypocalcemia which is associated to high serum phosphorus levels, and absent or inappropriately low levels of parathyroid hormone (PTH). [36] The low extracellular ionized (Ca^{2+}) may have a profound impact on the function of a large number of tissues and organ systems including the brain, muscles, kidneys and heart.[37,38]

In adults, the most common cause of HPT is parathyroid gland injury or inadvertent removal during thyroid surgery whereas in patients with thalassemias it is mainly attributed to iron overload, secondary to multiple blood transfusions and suboptimal chelation therapy.[36, 39-41]

The prevalence of overt HPT reported in 1661 TM patients, by the Italian Working Group on Endocrine Complications in Non Endocrine Diseases, was 3.6% [39], whereas a subclinical HPT, utilizing the nocturnal measurements of serum minerals, was observed in almost 100% of 13 TM patients, with normal morning serum calcium levels.[42]

HPT requires lifelong therapy with vitamin D or metabolites. Both under- and overtreatment can lead to unintended outcomes that can be irreversible. In undertreated or late treated patients with HPT, where there is a combination of chronic hypocalcemia and hyperphosphatemia, ectopic calcifications in organs may occur. [43,44] In over treated patient the risk of kidney stones and nephrocalcinosis is markedly increased. [45]

Conclusions

In conclusion, iron overload remains a critical problem, even in countries where chelation therapy is widely available and adequately implemented recently. An early recognition and prevention of the endocrine complications, by early and regular chelation therapy, is mandatory for the improvement of the quality of life of these patients.

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Heart disease in patients with haemoglobinopathies

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Hereditary hemoglobin disorders, also termed haemoglobinopathies, include mainly beta -thalasszemia and sickle cell disease and represent the most common monogenic disorders in human. Cardiac complications are still a leading cause of mortality and morbidity in patients with haemoglobinopathy, although heart disease due to either severe anaemia or iron overload have dramatically reduced in patient populations receiving modern regular therapy and follow-up (1,2). The spectrum of cardiovascular manifestations in haemoglobinopathies is wide and includes ventricular dysfunction, pulmonary hypertension, pericarditis-myocarditis, arrhythmias stroke and thromboembolic events.

The two main determinants of cardiovascular phenotype in haemoglobinopathy patients are the underlying molecular defect responsible for the main disease and the therapy applied for its management (3). In beta-thalassaemia, the basic defect is quantitative and concerns the reduction or total depletion of β-globin chain synthesis with a relative excess of α-globin chains that results in ineffective erythropoiesis. In sickle cell disease, on the other hand, the basic defect is qualitative, as a substitution at sixth amino acid in the β chain leads to the synthesis of an abnormal hemoglobin, hemoglobin S, instead of the normal hemoglobin A (4). The common denominator of both molecular defects is the development of chronic haemolytic anaemia, which, particularly when severe and untreated, leads to cardiovascular complications including left and right ventricular dysfunction and pulmonary hypertension (3). In addition, the applied disease-specific therapy may further modify the cardiovascular phenotype by preventing some complications while promoting some others (Figure 1).

Left ventricular dysfunction is the result of several pathophysiological mechanisms, of which high output state and iron overload are the most important ones. Other components of the complex pathophysiology of left ventricular dysfunction include vascular disease (structural and functional) and acute myocarditis. High output state is associated with chronic anaemia and increased percentage of hemoglobin F; significant and un- or mal-treated anaemia results in compensatory bone marrow expansion, while hemoglobin F binds to oxygen with greater affinity than hemoglobin A and as a result, there is a reduced tissue oxygen delivery (5). Iron overload cardiomyopathy is primarily seen in transfusion-dependent patients, namely those with thalassemia major or other haemoglobinopathies patients that require regular blood transfusions (*e.g.*, thalassemia intermedia). Repetitive blood transfusions, ineffective erythropoiesis, increased peripheral hemolysis, increased intestinal absorption and lack of proper iron chelation therapy are the main pathogenetic mechanisms associated with the development of iron overload cardiomyopathy (1,6). Iron overload causes further injury to liver and endocrine glands, while it is also believed to affect the immune system causing susceptibility to infections as well as the vascular function, effects that also contribute to the pathophysiology of iron overload cardiomyopathy (7). Acute myocarditis has also been reported as a cause of left ventricular dysfunction and heart failure in thalassaemia major. In addition, beta-thalassaemia and sickle cell disease patients seem to suffer from a complex vasculopathy. This vasculopathy involves both a functional component, characterized by endothelial dysfunction and increased arterial stiffness as well as a structural component concerning an elastic tissue defect similar to the one observed in hereditary pseudoxanthoma elasticum (8, 9).

Pulmonary hypertension is a leading cause of cardiovascular morbidity in haemoglobinopathies. In thalassaemia intermedia, pulmonary hypertension has been reported in up to 60% of patients not receiving blood transfusions, while in sickle cell disease, it is reported in up to 40% of cases (10). The pathophysiology of pulmonary hypertension is quite complex with several haemoglobinopathy-related factors and other non haemoglobinopathy-related ones holding key roles. Haemolysis, anemia and hypercoagulable state associated with the main disease represent two important factors in the pathogenesis of pulmonary hypertension, leading to increased pulmonary resistance and high cardiac output, while left ventricular dysfunction and pulmonary disease contribute further to the pathophysiology of pulmonary hypertension (10).

The right ventricle also seems to be affected by the above-mentioned mechanisms. Left ventricular dysfunction and pulmonary hypertension are important causes of secondary right ventricular dysfunction, while primary right ventricular cardiomyopathy has also been described in patients with thalassaemia major (11).

Regarding the clinical phenotypes of heart disease, high-output failure and iron overload cardiomyopathy are the two main forms of left ventricular cardiomyopathy. High output failure develops typically in thalassaemia major patients who not regularly transfused and therefore suffer from severe chronic anaemia. Iron overload cardiomyopathy is seen in regularly transfused patients with thalassaemia major that are not properly chelated. Thalassaemia major patients who are properly transfused and chelated have minimal or no heart disease. Pulmonary hypertension is the main cause of heart failure in patients with thalassemia intermedia who are not regularly transfused and is also found with a lower frequency and severity in patients with sickle cell disease (3). The leading cardiac complications in the different forms of haemoglobinopathies are summarized in Table 1.

All the mechanisms previously described set in frame the common pathophysiologic pathways in heart diseases in haemoglo-

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binopathies. The main two determinants of heart disease's phenotype are physician's therapeutic decision and patient's compliance with therapy. These two parameters are the most significant to take into consideration in order to prevent and manage cardiovascular complications in haemoglobinopathies (Figure 1).

Addressing the pathophysiology of haemoglobinopathies is the key to disease-specific therapy including blood transfusions (regular or upon demand) and iron chelation regimens (12). In thalassaemia major patients, regular blood transfusions to maintain a pre-transfusion level of hemoglobin ≥10 g/dL allows normal growth, prevents anaemia-related complications such as high output state, hypercoagulability and infections and ensures good quality of life (1,3). Iron chelation therapy prevents or manages effectively heart, liver and endocrine disease resulting from iron overload (3). In fact, iron overload cardiomyopathy is nowadays one of the few truly reversible cardiomyopathies. Modern therapy of thalassemia major, consisting of regular blood transfusions and iron chelation guided by cardiac magnetic resonance, has actually changed the course of the disease.

Many patients with thalassemia intermedia and those with sickle cell disease are in most cases non-transfusion dependent. Blood transfusions upon demand (in thalassaemia intermedia) or exchange transfusions (in sickle cell disease) in combination with iron chelation and/or hydroxyurea are considered as therapeutic modalities upon the development of disease complications (13,14).

As haemoglobinopathies are demanding clinical entities with multi-system complications, the need for multidisciplinary care in dedicated clinics is of outmost importance. Cardiovascular complications require special care and regular follow-up. In transfusion-dependent patients who develop cardiomyopathy and/or iron overload, as documented by cardiac magnetic resonance, regular blood transfusions aiming at haemoglobin ≥10 g/dL and combined inten-

Table 1. Leading cardiac complications in the different forms of haemoglobinopathies.

Haemoglobinopathy	Main heart disease
Thalassemia major, not regularly transfused	High output heart failure
Thalassemia major, not properly chelated	Iron overload cardiomyopathy
Thalassemia major, properly transfused and chelated	Minimal or no heart disease
Thalassemia intermedia, not transfused	Pulmonary hypertension
Sickle cell anemia Sickle thalassemia	Pulmonary hypertension Myocardial ischemia Strokes

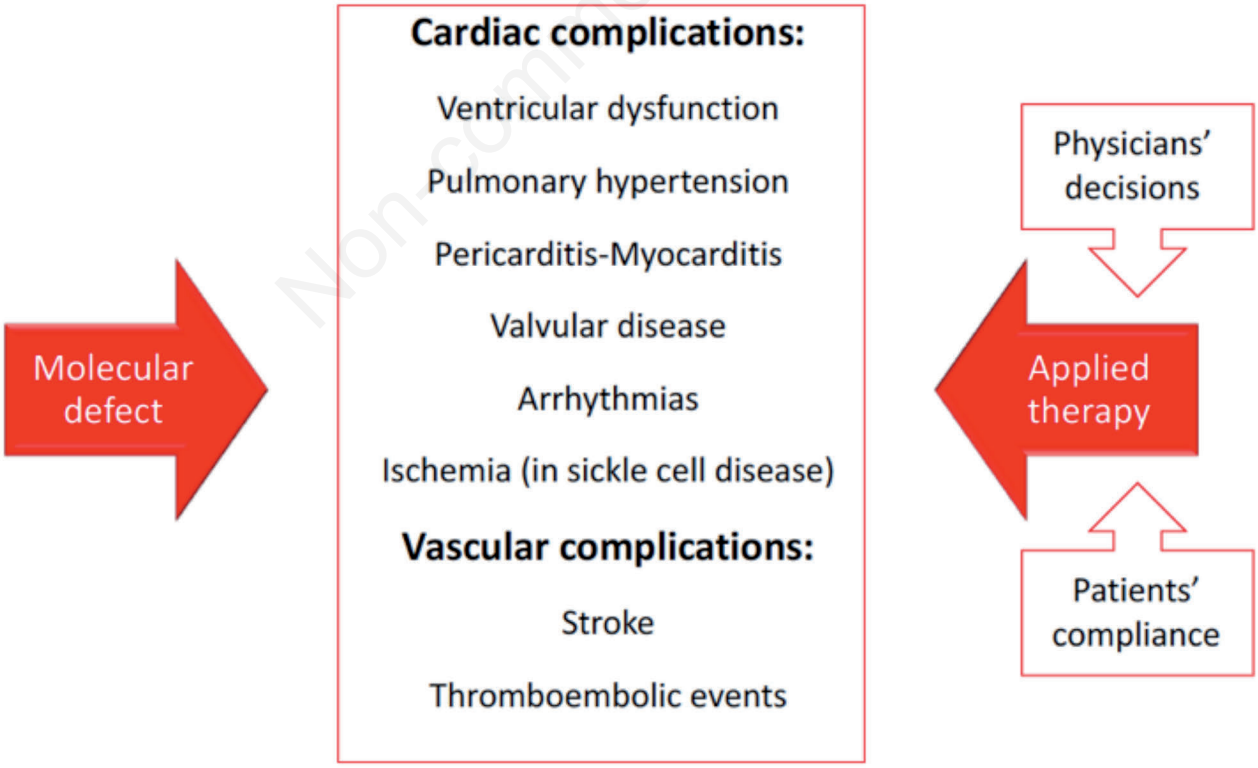

Figure 1. The spectrum of cardiovascular complications seen in patients with haemoglobinopathies is wide and crucially determined by the underlying molecular defect and the applied therapy.

sive iron chelation plus heart failure therapy (renin-angiotensin-aldosterone system inhibitors, β-blockers, diuretics, device therapy) are key stones in the management of those patients to improve symptoms and prognosis (3). It should be stressed the effect of cardiac magnetic resonance on the survival of those patients; it has been observed a 72% reduction of mortality due to timely diagnosis of iron overload since early 00's and a 62% reduction of all-cause mortality (15). A regular follow-up consisting of clinical examination, electrocardiogram, chest radiogram and echocardiography is suggested in all patients. In absence of heart disease, the follow-up is repeated annually and every 6-12 months in case of iron overload (3). Cardiac magnetic resonance is recommended in transfusion dependent patients and repeated according to the clinical course of heart disease. These timeline periods are indicative; on development or change of symptoms and on diagnosis of heart disease, cardiovascular assessment should be repeated according to the proposed algorithms (3).

Finally, treatment of endocrine and other comorbidities in incident haemoglobinopathies and lifestyle modifications that promote cardiovascular health (smoking cessation, regular physical activity, weight control) are also important for the prevention and management of cardiovascular complications.

To summarize, heart disease nowadays is not a leading cause of morbidity and mortality in optimally treated patients, thanks to disease-specific therapy and multidisciplinary management that render cardiovascular complication preventable. Even in the occurrence of heart disease, the early recognition and the effective management that current diagnostic and therapeutic modalities and the knowledge of pathophysiology of the disease offer make heart disease treatable. Regular cardiovascular monitoring in the context of multidisciplinary care and close collaboration with the haemoglobinopathy center are however warranted to ensure the above benefits accomplished by modern therapy and reduce further the morbidity of heart complication in these patients.

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Renal complications in thalassemia

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Abstract

Thalassemia is a disease with an extensive morbidity profile affecting almost every organ system. Renal involvement, once considered rare, is an underestimated and poorly studied complication that has been on the rise ever since medical advances granted patients longer life spans. Several studies and reports have emerged recently to shed light on the seriousness of this complication, although data is still lacking in terms of pathophysiology, diagnosis, prevention and treatment. In this review, we evaluate and compare renal involvement in the transfusion-dependent and independent variants of β-Thalassemia, highlighting the pathophysiology of kidney damage that involves iron overload, chronic anemia, and iron chelation therapy. An in-depth and focused review of the types of injuries incurred is also presented along with the diagnostic biomarkers accompanying each type of injury. Most research so far has focused on the transfusion-dependent thalassemia population being the group with most renal involvement, however recent reports have shown evidence of comparable, if not worse, involvement of the non-transfusion dependent population, sometimes leading to end-stage renal disease. As such, we try to shed light on distinct renal involvements in NTDT whenever available.

Introduction

The thalassemias are common monogenic disorders present worldwide. This inherited disorder of hemoglobin synthesis leads to an imbalance in *α/β*-globin production, which manifests as a chronic hemolytic anemia, ineffective erythropoiesis, and iron overload (IOL). Clinical presentation ranges from lifelong need of blood transfusions, to careful observation with minimal transfusions, to asymptomatic carriage. These are respectively coined transfusion-dependent thalassemia (TDT), non-transfusion-dependent thalassemia (NTDT), and thalassemia minor. However, with both TDT and NTDT, there exists a multimorbidity profile that stems either from the disease progression itself or from its long term managements (blood transfusions and iron chelators).[1]

The thalassemias have long been diseases of the pediatric population; nowadays, these inherited disorders present an equally significant burden among the adult population. The advances in both the knowledge and the care of this disease, as well as the increase in availability of treatments for those in need, have been factors for the aging of the thalassemic population. Such a change in demographics, however, allowed the recognition of complications associated with the longevity of patients living with thalassemia.[2,3] Long-term damage to the renal system has become evident with more studies targeting renal biomarkers and prevalence of different types of renal injuries in thalassemia. We discuss herein the renal complications found in thalassemia along with the role of iron overload, chronic anemia and iron chelation therapy (ICT) in their pathophysiology. The bulk of the literature tackles transfusion-dependent thalassemia patients, but information will also be presented on patients with non-transfusion-dependent thalassemia.

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Methods

Publications from potentially relevant journals were found on Medline and PubMed through advanced search option with "(thalassemia) AND renal". We excluded articles that cover other hemoglobinopathies unless they invoke a relevance to thalassemia. References of these articles were browsed and more articles were used if they improve understanding of the different aspects of the paper.

Mechanisms of renal complications

Chronic anemia, iron overload, and the use of specific iron chelators have all been linked to renal manifestations in patients with *β*-Thalassemia (Figure 1).[4] Although some studies on renal function in *β*-Thalassemia exist before ICT was adopted, the independent contribution to renal abnormalities by either chronic anemia or iron overload is harder to pinpoint, given their coexistence in the pathophysiology of the disease.[1,2,5,6] Other factors that can exaggerate this decrease in the thalassemic population may be glomerular diseases associated with hepatitis B or C and HIV infections (transfusion related), as well as iron-induced hepatic and cardiac dysfunction.[6]

Iron overload

Different mechanisms of toxicity from local iron in the kidneys are suggested. The nephrons may be exposed to heme and heme-containing proteins when the body is oversaturated with iron con-

taining elements from persistent hemolysis. Blood transfusions can further dump both non-transferrin bound iron (NTBI) and heme elements into the nephrons. Autopsy series on patients with TDT showed iron deposition in terminal portions of the proximal tubules and in the distal tubules.[7] Such hemosiderin deposits may pave the way for tubular necrosis, cortical atrophy, and interstitial fibrosis, which could be a factor in both acute and chronic kidney injuries in thalassemia. Iron itself plays a role in worsening the progression of chronic kidney disease (CKD), as studies on CKD individuals without states of iron overload showed a deceleration in CKD progression with the use of iron chelators.[8]

Iron is speculated to dissociate from transferrin in the acidic milieu of the proximal tubules, producing reactive oxygen species (ROS) that can damage the brush border of the renal tubular membrane. Even transferrin bound iron that enters the proximal tubular cells can still cause cellular damage by creating ROS once free iron is released upon lysosomal digestion.[9,10] Mitochondrial stress is linked to the resulting cellular injury, as it appears that an increased release of cytochrome C, lactate dehydrogenase and reduction in adenosine triphosphate (ATP) are noticed in damaged proximal tubular cells.[11] Oxidants also increase the susceptibility of glomerular basement membranes to damage by decreasing synthesis of proteoglycans, necessary for its integrity.[12]

In addition, tubulointerstitial damage may result when growth factors and cytokines are released from injured tubular cells, creating a bed for tubulointerstitial fibrosis and glomerular sclerosis.[13]

Chronic anemia

Renal tubular cells can equally be exposed to oxidative stress and lipid peroxidation from states of chronic hypoxia and anemia, even without iron overload.[14] The severity of anemia correlated well with markers of tubular abnormalities; the latter were reduced in the thalassemia major group with hypertransfusion regimens.[15] Mixed results however do exist.[16] Renal manifestations in NTDT patients who are ICT naïve could thus be the result of the interplay between chronic anemia and iron overload.

It is suggested that the decrease in systemic vascular resistance in the anemic state can instigate the increased renal plasma flow and subsequently the glomerular filtration rate (GFR), resulting in what is known as "glomerular hyperfiltration".[17] Such a phenomenon, reflected clinically as an increase of creatinine clearance (CrCl) or estimated GFR (eGFR), is usually associated with diabetes, hypertension or their precursor states. It brings about a state of glomerular hypertension, where glomerular capillary walls stretch and endothelial/epithelial injury ensues. Macromolecular leaks occur to relieve the intraglomerular pressure, but end up causing glomerulo-tubular dysfunctions like increased albuminuria and may lead to end-stage renal disease (ESRD).[18,19]

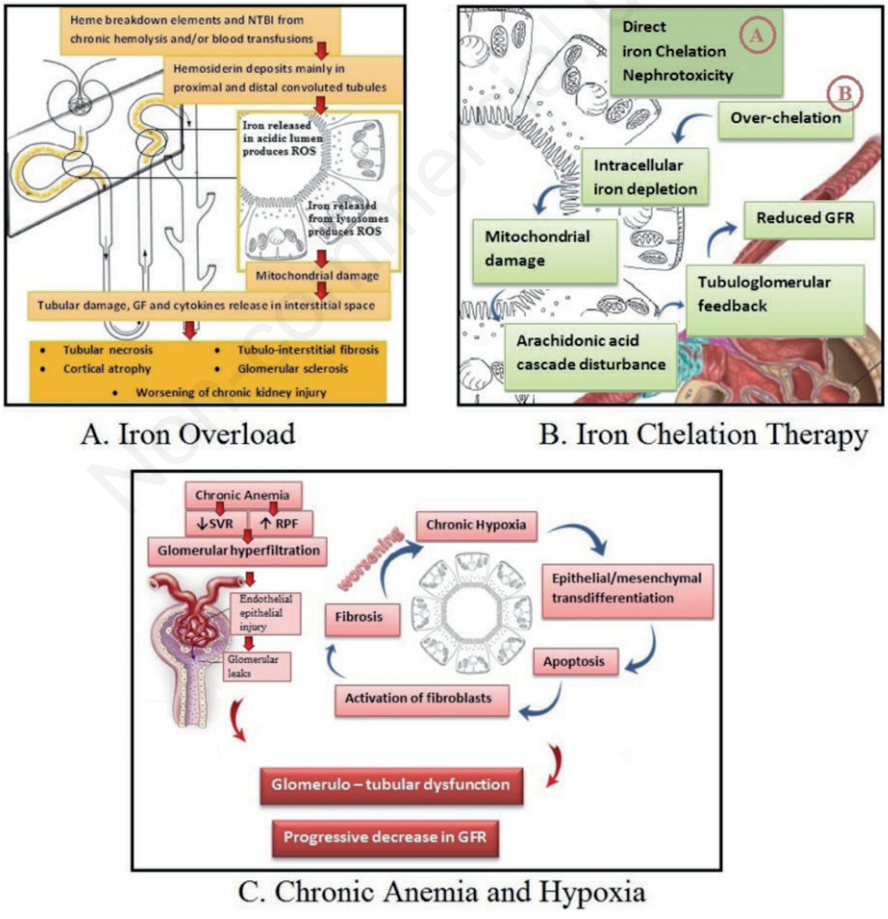

Figure 1. Pathophysiology behind the renal complications in thalassemia. (a) the suggested pathophysiology of renal disease due to iron overload; (b) two possible mechanisms for renal complications due to iron chelation therapy; (c) the impact of chronic anemia and hypoxia on kidney structure and function. NTBI, non transferrin bound iron; ROS, reactive oxygen species; GF, growth factor; GFR, glomerular filtration rate; SVR, systemic vascular resistance; RPF, renal plasma flow.

On the other hand, chronic hypoxia can throw tubular cells, whose metabolic demands are physiologically high, into a vicious cycle of epithelial-mesenchymal transdifferentiation, apoptosis, activation of fibroblasts and subsequent fibrosis. Fibrosis of the interstitial space then worsens oxygen diffusion, further propagating the tubular damage that was initiated by hypoxia. The aftermath can vary between tubulointerstitial injury, glomerulosclerosis and kidney fibrosis, especially in the setting of iron overload.[4,13,20] GFR would eventually decrease after prolonged cellular injury, possibly ending in ESRD.[19-22]

Iron chelation therapy

Management of iron overload in both forms of β-Thalassemia comes at an expense. Three agents are available for iron chelation - oral deferiprone (DFP), deferasirox (DFX), and the parenteral deferoxamine (DFO) - each with a spectrum of side effects. Kidney injury is a prominent side effect with DFX and DFO, especially when tight dosage monitoring is absent. Increased urinary excretion of beta-2 microglobulin and growth hormone after continuous DFO infusion suggests a role for over-chelation.[23] Direct nephrotoxic effect via tubular necrosis is the most likely mechanism of kidney injury according to biopsy findings and due to the reversible nature of the injury.[24] Additionally, over-chelation and depletion of serum iron has been hypothesized to play a role in renal damage. This has been supported by a trend of increasing serum creatinine in groups who showed significant decreases in liver iron concentration (LIC) and serum ferritin (SF) or in those with initially lower baseline iron indices.[4,25,26] Relative intracellular iron depletion is also theorized to trigger an imbalance between vasodilating and vasoconstrictive prostaglandins. This is due to tubular cell mitochondrial damage, reduction in ATP production and interference with arachidonic acid cascade, which can ultimately alter prostaglandin production and trigger tubuloglomerular feedback in favor of reduced GFR.[4]

Types of renal Injury

Kidney dysfunctions in thalassemia, namely TDT, tend to increase with age and correlate with risk factors (*e.g.* blood transfusion duration) or renal function biomarkers (*e.g.* hypercalciuria).[27] Many aspects of kidney can be affected, and these often coexist in the same patients.[28] More is known about TDT renal complications than NTDT at this point, as renal manifestations in NTDT patients are poorly described and data on the subject are scarce with lack of long-term follow-ups. So far, most studies on renal manifestations in this subgroup have revolved around the potential nephrotoxic effects of iron chelators.[4,29] It is very clear, however, that NTDT deserves comparable attention when it comes to renal outcomes.[30]

Tubular injury

There is evidence for tubular damage in the TDT population. Almost all patients are found to have low-molecular weight proteinuria at some point in time. Urinary markers of proximal tubular damage have been increased in several studies; these include N-acetyl-β-*D*-glucosaminidase (NAG) and β_2-microglobulin, calcium, phosphate, magnesium, uric acid, amino acids, and malondialdehyde derived from the destruction of membrane lipids by peroxidation (Table 1).[4,6,28,31-33] These markers, when compared to age-

Table 1. Frequency of positive renal biomarkers throughout studies in TDT, organized by renal injury types.

Renal Biomarkers	Range of frequency (%)
Markers of renal tubular injury	
Hyperphosphaturia	0-9.2
Hypercalciuria	0-79.2
Aminoaciduria	5.9-31.4
Magnesiumuria	8.6
Hyperaciduricuria	9.9-82.4
Urinary 2-Microglobulin	0-64.6
Elevated FENa	0-29.1
Urinary N-acetyl- -D-glucosaminidase (NAG)	35.9-100
Elevated Serum 2-Microglobulin	5
Elevated urinary retinol binding protein (RBP)	69.4
Elevated urinary alpha-1 Macroglobulin	54.8
Decreased urinary osmolarity	58.1-100
Markers of glomerular injury and GFR	
Elevated serum Cystatin-C	33.2-50
Glomerular hyperfiltration by eGFR	17.8-39.6
Decreased eGFR	0-58.82
Mixed glomerular/Tubular injury	
Proteinuria	0-90
Microalbumiruia	0-100
Others	
Hematuria	3.4-10.6

matched patients, are reduced in TDT patients who are cured by hematopoietic stem-cell transplantation.[34]

When urinary beta-2 microglobulin to creatinine ratio (BCR) was used to predict renal tubular damage, the use of alendronate was linked to less damage with TDT and NTDT patients. This however was in patients requiring alendronate as indicated for osteoporosis, and should be interpreted carefully, as cases of high dose bisphosphonates are known to cause proximal tubular nephrotoxicity.[28] When TDT and NTDT patients were compared, abnormal tubular function tests, including elevations in fractional excretion of sodium (FENa), urinary excretion of uric acid and alpha-1 macroglobulin (alpha-1M), were similar. However, retinol-binding protein (RBP), urine calcium/creatinine ratio ($U_{Ca/Cr}$) and BCR were higher in TDT while being respectively normal, normal and mildly elevated in NTDT. This might indicate that these parameters correlate better with blood transfusion, and perhaps iron overload mediated kidney damage.[30] Hypercalciuria (elevated $U_{Ca/Cr}$) evidently correlated with blood transfusions in a previous study in NTDT.[35]

Glomerular injury

Glomerular disease in thalassemia is related either to GFR or albuminuria.

Changes in GFR

Glomerular filtration rate is reportedly elevated in TDT patients as compared to age-matched healthy individuals.[35,36] Glomerular hyperfiltration can range from 20 to 40% of thalassemia cases.[28,35] Male gender and a previous history of splenectomy were found to be independent predictors in multivariate analyses.[28] In NTDT patients, anemia may prove pivotal in the observed renal hyperfiltration. Regular blood transfusions decreased this phenomenon, but were also linked to increased hypercalciuria. This strengthens both the role of chronic anemia/hypoxia in the pathophysiology of glomerular hyperfiltraion, as well as the role of blood transfusion in some aspects of tubular dysfunction.[35] Glomerular hyperfiltration might be an early hallmark of NTDT renal manifestations. A retrospective study of 50 NTDT patients revealed glomerular hyperfiltration to be present early in the course of the disease with nearly half of the patients exhibiting this finding. Importantly, age negatively correlated with GFR. Within the upcoming years, around 60% of these patients had abnormal urine protein to creatinine ratio (UPCR) of ≥200 mg/g, and 14% developed proteinuria with UPCR >500 mg/g. Proteinuria positively correlated with higher levels of LIC and NTBI.[29] However, contrary to diabetic and hypertensive glomerular diseases, little evidence exists so far to claim that hyperfiltration in thalassemia is indeed a harbinger for future renal damage, as it is merely explained by the physiological hyperdynamic compensation in anemic patients, which is understandably larger in a male habitus or in splenectomized patients.[28] Long term follow-up studies may validate this assumption.

Although decreased GFR is rarely documented at pediatric age, gradual decrease can creep up with progressive renal damage, and it can start appearing in adult patients.[37] 18.5% of adult thalassemic patients had eGFR <90 mL/min by the end of a 10 year follow up study. This decline in eGFR was more significant in patients with tubular damage.[38] Decreasing GFR might reflect accumulating long-term damage to the kidneys. This follow-up however was in a period without proper blood transfusion guidelines, and when iron chelation was still widely inadequately used. More recent cohort studies are required.

Albuminuria

Different studies used different cut-off values of albumin to creatinine ratio (ACR), and even different biomarkers, to detected proteinuria as a marker for glomerular damage, making it difficult to interpret discrepancies. In pediatric TDT patients, proteinuria ranged from 24% to 47%, and did not change with deferoxamine therapy.[39,40] Significant glomerular proteinuria in adult patients was 20% using ACR, but was found to be 33% in another study using serum cystatin-C.[28,31] Comparison of TDT *vs* NTDT revealed elevated serum cystatin-C and spot ACR levels in both groups compared to general population, but no clinical significant difference amongst them was found.[30] When ACR was used in TDT and NTDT patients, T2* value ≤20 msec on cardiac magnetic resonance was the only independent predictor for glomerular dysfunction; it was not associated, however, with renal tubular damage or hyperfiltration. A possible link between cardiac disease, renal dysfunction and iron overload in thalassemia could be suggested, but this requires further targeted studies that include measurements such as NTBI or free oxygen radicals in the serum.[28] There is still a debate over the link between ICT, mainly deferasirox, and glomerular disease.[28,39]

ICT-mediated acute kidney injury

Although rare, acute kidney injury (AKI) has been attributed to ICT.[41,42] AKI has been reported in 40% of patients on DFO. This mostly occurred with the intravenous method of administration following overdose of the drug due to malfunction of the pump and/or inadequate monitoring during treatment. AKI, should it occur under such cases, appears to respond well to high-efficiency hemodialysis.[43,44] Several cases of AKI have also been reported in the post marketing surveillance of DFX.[4]

In a multicenter randomized phase 3 trial comparing deferasirox and deferoxamine in TDT patients, a dose-dependent increase in serum creatinine was observed in 38% of patients receiving DFX, and a similar increase was observed in 14% of patients on DFO. The increases were mostly within normal range and never exceeded twice the upper limit normal (ULN). In most patients receiving DFX who experienced elevated serum creatinine, levels spontaneously normalized and thus dose reduction was only required in 13% of patients.[25]

To determine if the elevated creatinine level was progressive, the outcome of 1074 iron overloaded thalassemia patients treated with DFX for one year was reviewed. 10% of the patients experienced a rise in serum creatinine (>33% baseline or >ULN) on two consecutive measurements. Most of these patients had high baseline serum creatinine levels. One case of AKI was reported. Overall, there was no progressive increase in mean serum creatinine.[45] In parallel, another study that investigated cystatin C levels in TDT patients receiving DFX demonstrated stable levels over the 9 months period of the treatment.[46]

Renal hemosiderosis

Although iron deposition is documented in biopsied tubules of TDT patients, iron detection on magnetic resonance imaging (MRI) R2* for adult patients was closer to the healthy population group as compared to sickle cell disease (SCD) patients. The mechanism for anemia in SCD is intravascular hemolysis as compared to ineffective erythropoiesis in thalassemia; this may play a role in the difference of outcomes.[47] Renal parameters, mainly markers of tubular dysfunction, have correlated, albeit conflictingly, with serum ferritin and LIC, as well as with iron chelation therapy use, suggesting a possible impact of iron kidney accumulation on the renal function.[16,48,49] For example, Increases in NAG and β2-M are higher in patients with high serum ferritin levels, and chelation therapy showed reversal of the findings.[33,49] More recently, 77% of a group of adult TDT patients showed evidence of hemosiderosis on kidney MRI T2*. 51.5% of the same group showed

decreased eGFR.[31] This could reflect that minimal iron accumulation can have an impact on renal function, but as more accumulation becomes detectable on MRI, kidney function can worsen. Further studies are needed to prove such correlations.

End stage renal disease

In a cohort of 127 NTDT patients, 4% developed ESRD that required regular hemodialysis. A review of their medical charts over a 10 years observation period revealed that elevations in serum creatinine and dipstick-positive albuminuria were the first manifestations of renal disease.[22] One patient with nephrotic range proteinuria was found to have focal segmental glomerulosclerosis (FSGS) on renal biopsy. Iron overload and paradoxically excessive iron removal, as well as the hemodynamic maladaptation related to anemia with resultant hyperfiltration, have all been suggested to gradually result in tubular atrophy and eventual glomerulo-interstitial fibrosis.[4,6,38,50]

Fanconi sydrome

Renal wasting of electolytes, amino acids and glucose occurs in thalassemia, and it is most likely a tubular dysfunction.[33,51] Deferasirox, which is minimally excreted in the kidneys, is linked to fanconi syndrome (FS), a heightened form of proximal tubular wasting manifested by hypophosphatemia, normal anion gap metabolic acidosis, glucosuria, and proteinuria. During clinical trials with DFX therapy, FS was a rare complication, occurring in 0.1 to 1% of patients.[25,52] It is postulated that deferasirox's lipophilic properties allow it to penetrate cell membranes and to accumulate in the proximal tubular cells. This can either cause direct nephrotoxic effects or deplete mitochondrial iron, with resulting proximal tubular dysfunction. To date, more than 14 cases of FS (mostly β-thalassemia patients) have been reported secondary to DFX therapy.[53-55] Management includes discontinuation of DFX and hospitalization for fluids and electrolytes repletion. Among three re-challenge attempts, one patient had recurrent tubulopathy leading to permanent discontinuation, while the other two required long-term electrolyte supplementation when restarted on a lower dose.[56,57] Plasmapheresis did not appear to be helpful in a case of acute deferasirox toxicity.[55] Monitoring guidelines for DFX therapy do not suggest monthly testing for serum electrolytes and urine analysis, and therefore detection is delayed until patients are symptomatic and need hospitalization for management. Given that most patients affected with DFX tubulopathy are at the higher end of the dosing range, it is advised to check serum electrolytes at baseline and every 3 months following initiation of therapy. Prompt withdrawal of DFX and referral to a nephrologist is advised with laboratory evidence of electrolyte abnormalities.[58]

Urolithiasis

Transfusion-dependent thalassemia patients have a higher occurrence of both asymptomatic (59%) and symptomatic (18%) kidney stones compared to the general population. Stones have a mixed composition but they are most commonly calcium based. The latter are associated with lower femoral z-scores on bone marrow densitometry; calcium stone formers were also found to have lower ferritin levels and higher serum creatinine levels.[59] Hypercalciuria and proteinuria also commonly co-exist with urolithiasis, and hypercalciuria strongly correlated with deferasirox body-adjusted dose, paralleling previous studies.[60] Data from a 19-year longitudinal study shows that a switch from deferoxamine to deferasirox is associated with faster bone resorption.[61] All these notions hint at deferasirox use as a link between bone and kidney manifestations in thalassemia. Among other stone types, thalassemic patients frequently form cysteine stones, and the reason could lie in an underlying tubulopathy. Moreover, the occurrence of struvite stones may warrant searching for undetected chronic kidney infections, especially in the splenectomized patients.[59] Hematuria has ranged from 3.4 to 10.6% in observational studies on TDT and NTDT patients, and it is mostly attributable to asymptomatic kidney stones.[32,62] Splenectomy, with the subsequent high erythrocyte turnover, is associated with higher rates of nephrolithiasis in NTDT.[63]

Detection, prevention and management

There is a trend towards earlier detection of glomerular and tubular abnormalities, especially in pediatric thalassemic populations, using early biomarkers of renal dysfunction. Table 1 and supplement 1 report the frequency and range of abnormal renal biomarkers from studies on thalassemia variants.[15,16,27-33,35,36,39,40,51,59,64-72] ACR and BCR can predict initial signs of glomerular and tubular impairment, respectively, in the general population; their use in many aforementioned studies reflects their validity in the thalassemic population.[28,73] Serum cystatin-C and serum or urinary beta-2 microglobulin have received attention as better tools to assess sensitive changes GFR and creatinine clearance in thalassemia as compared to serum creatinine and eGFR.[16,39,46,72,74-76] Serum cystatin-C is filtered by the glomerulus, but is neither secreted nor reabsorbed by tubular cells, so it is also a reliable marker for glomerular dysfunction, while beta-2 microglobulin is filtered but almost completely reabsorbed by the tubules, giving its importance in screening for tubular abnormalities.[39] It seems that these markers may independently correlate with serum ferritin, transfusion rate, duration of chelation therapy, albumin/creatinine ratio, serum creatinine, LIC and age, while also negatively correlating with eGFR, creatinine clearance, and hemoglobin.[21,22,35] Serum cystatin-C is high in thalassemia minor but higher in NTDT and TDT groups as compared to healthy patients; this suggests its possible value as an early precursor of glomerular dysfunction in patients with thalassemia.[30] NAG is another marker worth use as it correlates with proteinuria.[27,72,77] Hypercalciuria, tested by urine calcium to creatinine ratio, is consistent within many studies with proximal tubulopathy. It correlates best with blood transfusion burden and deferasirox body-adjusted dose.[31,35,40,59,61,68] But it could also be found in patients who are not blood transfused and should be carefully assessed with concomitant mineral bone diseases.[30,33,68,78,79] Conflicting data prompt creating meta-analyses which can provide conclusive correlations and strong diagnostic statistical parameters for these biomarkers;[28,36,46,76,80] However, these are difficult to achieve due to many reasons (Table 2). UPCR remains an important and frequently used marker for glomerular dysfunction.[30,68,78]

eGFR (using the Schwartz Formula) might not be an accurate assessment in thalassemia, as some studies suggest it overestimates the actual filtration rates when compared to 24-hour urine creatinine collections, especially in states of hyperfiltration.[27,35,67] eGFR and serum ferritin have been correlated with tests like FENa, beta-2 microglobulin, UPCR and cystatin-c, but alone they are not good enough predictors of renal outcomes.[28,30]

Studies show opposing relationships between FENa levels and renal disease severity in beta thalassemia patients.[27,30,33,68,76,81] Age difference of study groups and its implication on renal dysfunction might play a role in the different results, but systemic analysis is needed to prove this.

Urinary RBP is a specific marker for tubular dysfunction, even in the presence of massive proteinuria. Alpha-1M and RBP still have limited data in thalassemia screening for renal function, but they do show reliable results. RBP stands out in being elevated only in TDT as compared to other factors that are equally elevated in NTDT as well.[30,82]

Table 2. Factors hindering proper meta-analyses for renal biomarkers in thalassemia studies.

Factors affecting proper meta-analysis construction for renal biomarkers in thalassemia
Majority of studies have small sample size (<10 to 500)
Different parameters and definitions are used for different renal injury markers
Different techniques are used to detect same biomarkers across studies
Populations studied are not homogeneous (age, ICT use, transfusion burden, splenectomy, hemoglobin levels, iron overload status)
Studies do not account for concomitant medication (calcium, vitamin D, ICT, etc.)
Observational studies present data in different methods (incidence of abnormalities *vs* average value of tests), affecting uniform information collection
Other kidney diseases can affect results and not always accounted for (hep C, diabetes, etc.)

Table 3. Guidance for management of renal issues with iron chelation therapy.

Issue	DFO	DFP	DFX
Pre-cautionary	Monitor patients for changes in renal function	Special care must be taken in patients with renal impairment since studies have not been conducted to evaluate its safety and efficacy in these patients	Measure serum creatinine and CrCl before starting therapy; Monitor serum creatinine regularly
Baseline renal impairment	Contraindicated in patients with severe renal disease or anuria	DFP has not been evaluated in patients with renal impairment	Impairment of CrCl 40–60 mL/min: reduce starting dose by 50%; do not use if serum creatinine >2× ULN or CrCl <40 mL/min
Increased serum creatinine	Monitor patients for changes in renal function; increased serum creatinine, acute renal failure, and renal tubular disorders have been reported in postmarketing studies	(No guidance provided)	Treatment should be interrupted or reduced if increase is >33% above baseline at 2 consecutive visits (and above the age-appropriate ULN in pediatric patients)
Continued renal impairment	(No guidance provided)	(No guidance provided)	Discontinue therapy if CrCl<40 mL/min, or serum creatinine >2× age-appropriate ULN

So far, according to the thalassemia international federation (TIF) guidelines of 2014 for TDT management, periodic chemistry panel, urea and creatinine should be done every 3 months (monthly if on DFX). Urinalysis is to be done biannually.[3] Since iron overload, chronic anemia and improper ICT use are all linked to renal complications, the judicial use of blood transfusion and iron chelators, along with proper follow-up testing, is recommended. It is always important to rule out and manage other diseases that can affect the kidneys, such as diabetes, hypertension, etc.[4] Table 3 aids in the choice and monitoring recommendations when using iron chelation therapy. [83-85]

Conclusions

Renal disease is a long-term complication that should be recognized in thalassemia, especially with the rise in the average age of this population. Proper assessment of renal function abnormalities in thalassemia can be challenging because of the increased use of iron chelators, which themselves can affect renal function. With increasing information concerning the renal abnormalities and convenient renal biomarkers, good meta-analyses can shed light on the best tools to use for assessment and prevention of renal disease in thalassemic patients. However, definitions and markers of kidney disease across the studies are highly heterogeneous, and most studies available are cross-sectional, involving a small number of patients. More longitudinal data is required to fully portray any possible differences between TDT and NTDT abnormalities, as well the current prevalence of these diseases in the era of new iron chelation and blood transfusion guidelines. With enough data still lacking, there is a need for close monitoring and follow-up of renal function in NTDT patients as they live longer, and this puts them at increased risk of severe renal disease. Progress of research in this topic will allow the detection of renal dysfunction harbingers in hope to arrest the progress of renal injury, if not to reverse it.

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Challenges to management of pain in sickle cell disease

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Abstract

Sickle Cell Disease (SCD) is one of the most common blood disorders in the world. Pain is the primary reason for which individuals with SCD interact with the healthcare system. Generally speaking, there are two types of SCD pain: vaso-occlusive pain (or sickle cell disease crisis) and chronic pain caused by an accumulation of organ and tissue damage over time. However, despite its frequency, we have limited understanding about what causes pain in sickle cell disease, how best to manage pain in SCD and (most importantly) how to prevent pain in SCD. For medical providers, pain is also an elusive target due to the difficulty in objectively measuring pain and the importance of relying on patient reported outcomes. To face the challenges in managing pain in SCD, we will review the current understanding of the pathophysiology of vaso-occlusion, the multiple dimensions of the pain experience, and the current methods of measuring and managing pain. We will also review new pharmacologic agents undergoing clinical trials in SCD that will help to prevent pain and improve outcomes in SCD.

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National policies in ensuring access to quality and safety of drugs: A challenge or a prerequisite

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Abstract

Access to the essential medicines is an important challenge in the developing countries. To have access to the quality and affordable medicines, the pharmaceutical decision makers try different strategies. The production of generic and copy medicines is one of the strategies that if adopted based on the recognized standards and norms can be effective in raising the health status in the developing countries. However, the regulation enfeeblement has somewhat impaired the quality of generic and copy medicines and harmed the health life of consumers. Here we aim to reflect over the role of different beneficiaries including international organizations, governments, pharmaceutical companies, and NGOs in ensuring the feasible and sustainable access of citizens to the essential medicines. We also aim to highlight the importance of the patient status in the enhancement of the medical delivery.

Introduction

The UN Secretary-General reported that more than 2 billion people across the globe lack the (adequate) access to the essential medicines (1). This alone shows what a challenge it is to ensure the distribution of and the adequate access to the essential medicines. The difficulty in the access to the appropriate healthcare has lowered the life expectancy on the average 32 years below the developed countries; in other words, the average life expectancy among the developed countries is 1.7 times higher (2). The findings show that the share of out of pocket payment in developing countries with lower income is higher than that of the developed countries (3). Paul Van Hoof (European Federation of Pharmaceutical Industries and Associations (EFPIA)) holds the belief that spurring innovations can lead to the better disease management and the higher life expectancy. Likewise, Director General of Medicine for Europe believes in competition as the key for the price drop and the better access to medicines in the EU zone.

Thalassemia major is the disease prevalent at a region in the world known as the thalassemia belt (5). The ones being located within this belt are mainly the developing countries faced with the challenge of access to the essential medicines. In recent years, the governments have adopted different strategies to increase access to the essential medicines; the strategies have been mainly based on the health cost reduction formulae including the production and distribution of generic and copy medicines. This approach has not been always effective though and has evoked negative reactions by patient advocacy institutions (4). Here we try to address the various ways for higher patient access to the essential medicines and the role governments, NGOs, and pharmaceutical companies would play to this end.

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The world outlook for the pharmaceutical market

After the enactment of Hatch-Waxman Act in 1984, the competition in the pharmaceutical market made the price changes. This persuaded the pioneer companies to produce more newly formulated medicines on one hand and restructure the formulating models for more generic medicines to be made available on the other. So much so that in 2009 generic medicines accounted for approximately 75% of the prescriptions in the US.

Before the Act, the producers were required to demonstrate the efficacy and safety of generic medicines by independent and unbiased reviews. However, the multiple performances of time consuming and costly clinical trials hindered the timely market availability of generic medicines and raised the production cost. On the other hand, the Act made the US pharmaceutical market open to generic medicines and paved the ground for competition and the price balance.

The availability of generic medicines placed much impact on the market share of brand-name drugs. As shown in Figure 1, the share of brand-name drugs during 12 months after the generic medicines entered the market (1999-2000) was about 68% while this rate within the 12-month time frame of 2007-2008 reached 37% in the first month and dropped to 15% in the final month. The figure 1 clearly displays the changing trend of health structures in the US towards the consumption of generic medicines (9). Therefore, the higher use of generic medicines in the US and subsequently in the other developed countries is the projected future change.

Based on the forecast estimations for 2016-2020, the end of the "patent for small molecules" era would place a remarkable impact more than the preceding years on the increasing production cost in the developed countries and pharmerging markets (10). The years 2005 to 2012 witnessed the significant changes in the share of generic and brand-name drugs in the world market so that the market share of the latter has faced significant increase prompting health advocates and investors and beneficiaries to aim at reversing the expenses (Figure 2) (11).

Besides the big and vanguard companies are run in the countries like Switzerland and the States that do not succumb to TRIPS Agreement and that is why the prices of brand-name medicines are much higher than the generic (12). Thus, the developing countries are persuaded to produce generic and copy medicines.

Generic medicines: is the quality assured?

The US FDA defines the term generic as "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use". Bioequivalence is then considered as one of the most important elements in the production of generic drugs. The producers of generic drugs based on the FDA Guidance are obliged to prove the equivalence of the main pharmaceutical ingredients and the comparability of their products to brand-name or reference medicines (13). Nevertheless, there has been always a trust challenge in regard to generic drugs with fueled concerns; the less efficacy and more side effects of generic drugs compared with the original brand-names are the concerns that would be eliminated if the international norms and standards of production are met for the quality to be ensured. In the countries like the States where food and drugs are supervised by the entities with organizational clarity, the consumption of generic drugs has been on an increasing trend with 7 medicine prescriptions out of 10 being generic.

However, in developing countries the trust in quality is enfeebled and further impaired with the lack of a clear-cut distinction between the production and supervision. The study conducted by Heritage Foundation and the Wall Street Journal shows the countries located on the thalassemia belt particularly in the Middle East, North Africa, and the Persian Gulf region having scored lower than 60 for "Index of Economic Freedom" that poses a higher risk for responsibilities of quality supervisors and producers to be mutually interfered (15).

At the same time, the researches done on developing countries stipulate the inability of regulatory bodies in a broad range of themes that if the otherwise would ensure the safety and efficacy of medicines (Table 1)(16). In fact, the worries about the quality of generic drugs still persist wide range and spur concerns among thallasemics (17).

Conclusions

Despite the significant role of generic drugs in the medical care of patients especially chronically ill patients, concerns alarm on the quality particularly in developing countries and the ones with

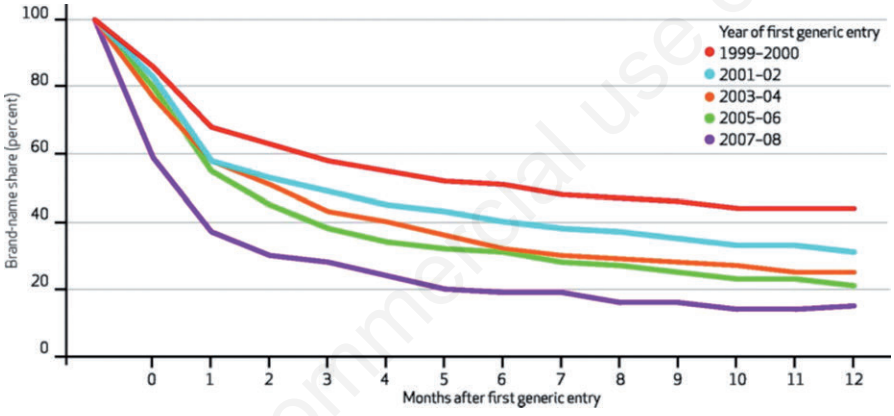

Figure 1. The share of brand-name drugs during 12 months after the generic medicines entered the market.

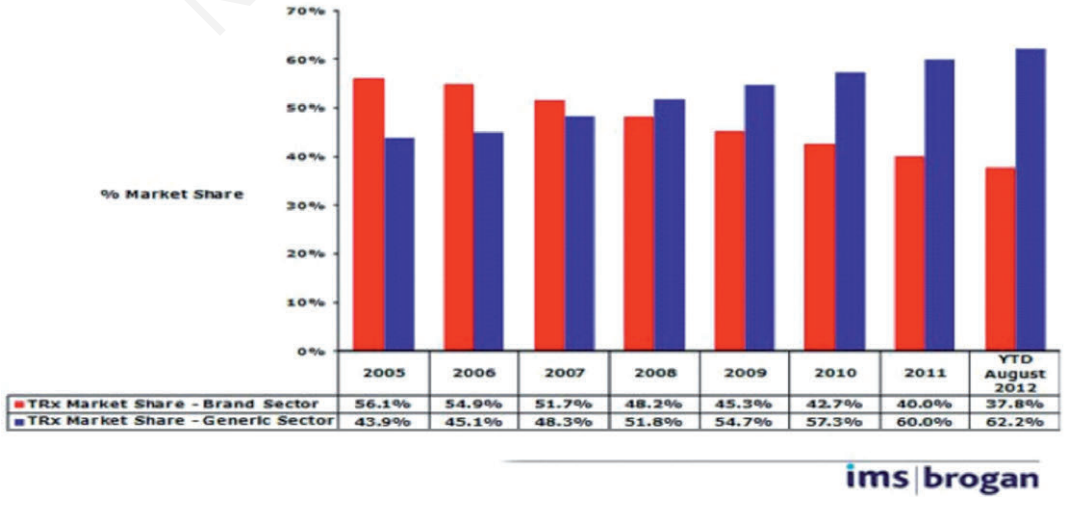

Figure 2. The changes in the share of generic and brand-name between the years 2005 and 2012.

Table 1. Comparison of key regulatory authority of a few developing countries.

Country	Legislative and regulatory framework	Pharmaco vigilance	GMP compliance	Quality and safety control
Argentina	Medium-Low	Low-Medium	Medium	Low-Medium
Brazil	Medium-High	Medium	Medium	Medium-High
Egypt	Low-Medium	Low-Medium	Medium	Medium
China	High	Medium	Medium	Low-Medium
India	Low	Low	Low-Medium	Low
Peru	Low-Medium	Low-Medium	Medium	Low-Medium
Russia	Low-Medium	Medium	Low-Medium	Low-Medium
Thailand	Low-Medium	Medium	Low-Medium	Low-Medium
Turkey	Medium	Medium-Low	Medium	Low-Medium

lower levels of economic freedom. Thallasemics are lifelong consumers of the essential drugs access to which is the most important lifelong challenge. Patient Centered Care suggests the delivery of the adequate and precise information to the recipients of medical services as the priority of the health system. Emotional support for patients is also planned to be a part of the care programs (18). It is therefore imperative to assure patients of the quality of the consuming medicines and avoid the Hobson's choice prescription of the medicines whose quality is in doubt.

To reach the favorable quality, WHO has issued a guideline whose abidance is obligatory for both developing and developed countries. NGOs are likewise responsible for the activities of pharmaceutical companies to clarify. The best example is Bill and Melinda Gates Institute that innovated "Access to Medicine Index" program by which the big pharmaceutical companies were provoked to be accountable and issue licenses to developing countries (20). The Gilead Company licensed its hepatitis C drugs to India and made the prices drop in Egypt thereby expanding access to the essential medicines (21, 22). Thus, the role of NGOs is significant in the clarity about the medicine quality and the changes in the price of brand-name medicines particularly in developing countries.

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Adherence to treatment: Doctor *vs* patient perspective

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Abstract

It has been demonstrated over time that patients with haemoglobinopathies who exhibit a high level of compliance to proper therapy benefit not only from higher life expectancy but also from significantly better quality of life. The treatment of thalassaemia consists of blood transfusions and iron chelation therapy. Managing any complications due to iron overload, performing all necessary clinical and laboratory examinations and dealing effectively with psychological issues are also very important. Blood transfusion scheme must be designed by the treating physician according to the patient's clinical needs. Chelation therapy should be aimed at selecting the right medication and the right dose. Examinations should be as organized as possible, and the management of complications depends significantly on cooperation with experienced specialists in each respective field. Ultimately, effectiveness of treatment and patient's psychological well-being (acceptance of the disease and positive attitude) are the most decisive factors, as they seem to be connected to adherence through a mechanism of positive feedback. Hence, professional psychological support should be part of multidisciplinary care. Difference of point of view between doctor and patient can often be the reason behind misinterpretations or misunderstandings.

Introduction

The treatment of thalassaemia may often seem to a patient like an endless, repetitive procedure that gives the feeling of little, if any, advancement. Due to constant iron overload caused by regular blood transfusions, a steady chelation therapy scheme is important for the patient to maintain relatively steady body iron levels. However, no therapeutic scheme can be effective unless the patient adheres to it properly. The core management of thalassaemia patients is well described as well as the management of complications such as those occurring in the heart, liver or endocrine organs; however there is still relatively poor understanding, or even the perceived need, to tackle the complex psychological issues pertaining to acceptance of the disease and its repercussions, as well as maintenance of a healthy image of oneself.

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Discussion

The two main aspects of treatment of thalassaemia are transfusion therapy and iron chelation. A proper transfusion scheme must be designed for each patient individually by the treating physician, tailored not only to his clinical needs but also to important aspects of his personal life (including activities related to work, education and family), so as to ensure minimal interference. Blood unit being ready for administration upon patient's arrival is a very effective measure in minimizing patient's distress. Of course, it requires communication and coordination between patient and hospital. Chelation therapy is more challenging. Selecting the optimum regimen (monotherapy with one of the three chelating agents available so far, or a combination of some of them) should take into account clinical status of the patient as well as his preference and his daily activities, and also perhaps availability and cost of medication. Patients should not be discouraged to try different regimens, which may offer them not only adequate chelation but also better quality of life, always under proper supervision. Determining the right dose may often involve a certain level of experimentation and close follow up. Insufficient or excessive doses can lead to iron accumulation and toxicity respectively, which constitute negative experiences for patients and threaten the relationship of trust between patients and doctors.

Patients should feel free to discuss openly about failure to comply without the fear of facing negative attitudes. Management of complications from various organs and/or systems (*e.g.* cardiac, hepatic, endocrine complications, etc) should be done with close collaboration between the doctors of the thalassaemia unit and experts in each respective field with experience regarding thalassaemic patients. Ideally, a multidisciplinary team should meet and discuss patients, particularly those with complex needs on a regular basis. Moreover, any non-urgent clinical and laboratory examinations needed should be well organized in advanced in order to minimize patients' distress and anxiety, as well as interference with other activities. Ideally, they could be performed on the same days as transfusions as much as possible. Last but not least, psychology plays a major role in compliance. That is a very complex issue, affected by multiple factors (family, society, culture, mentality of each individual patient, etc) that may often need to be addressed through professional help from psychologists, who could be members of the multidisciplinary team. Patients who face problems accepting themselves are often trapped in the stages of grief (Kübler-Ross model), also find it difficult to accept the necessity for proper treatment. It is important to emphasize the impact that the doctor of thalassaemia unit can have over patients. Depending on the approach, a patient may be inspired to pursue better treatment, or feel negativity towards it. Support groups can be formed even spontaneously among patients sharing experiences, knowledge and concerns. Patients with successful adherence to treatment can be viewed as role models by others, whereas patients with low adherence and subsequent aggravating consequences can be viewed as examples to be avoided.

Conclusions

The demanding aspects of thalassaemia's treatment as well as the plethora of complex factors that affect a patient's personality and psychological status make proper adherence challenging. A holistic approach by an experienced multidisciplinary team is required, as well as well-organized treatment schemes that will cause minimal interference to patient's lives. A relationship of trust and good communication between patient and doctor is essential in order to avoid misunderstandings due to difference of point of view. Psychological support by other patients or healthcare professionals such as psychologists may be needed for some patients.

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Patient care: Unmet needs globally

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Introduction

Literature demonstrates that long survival and a good quality of life are achieved where the patients' needs for holistic care are recognised and the appropriate services are offered. The once fatal diseases of childhood have become chronic conditions of adult life. [8, 9, 10].

TIF's mission is to promote and assist in the implementation of national programmes for the treatment of thalassaemia and other haemoglobin disorders, wherever the patients may be residing, driven by the vision of equal access to quality healthcare for every patient [1].

The purpose of this paper is to report on preliminary results of a global TIF survey that sought to examine the inequalities, which patients experience in their management by services and professionals across the world, and identify some of the reasons contributing to such inequalities. Emphasis in this investigation is given to the services that are offered from the patients' point of view. This work derives from, and is part of TIF's ongoing relationship with its member associations, individual patients, as well as health professional and health authorities.

A framework for mapping and evaluating thalassaemia patients' needs for holistic care

In an attempt to identify inequalities, we sought for knowledge of the requirements for an optimal system for the care of haemoglobinopathy patients [2, 3, 4, 5]. These requirements are dictated by the nature of genetic chronic disorders:

- They are hereditary, and therefore there are implications on pre-conceptual issues, such as parents being aware of their carrier status, since these are Mendelian recessively inherited conditions, prior to the decision to have children. This presupposes a well-informed public, and an adequate counselling system.
- They present in infancy or at the toddler age group and, in the absence of a cure, they must be managed throughout life.
- Vital organs of the body are affected and if not identified early on through a clinical monitoring system, and dealt with according to current evidence-based guidelines, serious and life threatening complications develop.
- Coordinated, multidisciplinary care is a basic requirement, and if provided throughout life, will result in the best possible outcomes. Results are best if the patients are treated in designated expert centres [6].

From these characteristics, including the pathophysiology, multi-organ involvement and natural history of haemoglobin disorders, certain conditions must be fulfilled to support optimal care, able to achieve the outcomes that are hoped for. These conditions or ingredients can be summarised as follows:

1. Free or affordable healthcare based on country income: Lifelong, expensive treatment with regular blood transfusion, iron chelation medication and involvement of specialised and multidisciplinary services, cannot be sustained by the average family income. This is particularly so in countries with poor economies. In Bangladesh for example, the direct medical costs range from 1632-3960 USD per year, while over 72% of patients' families have an annual income of 1536-3000 USD, and so cannot possibly provide for their children, while there is no government or other health insurance support. The richest will survive! [11]. The estimated costs are reported quite differently in various countries – in Iran for example, the average annual cost was estimated to be 8322 USD [12] but in this country the governmental support is much higher. Out of pocket expenses can be catastrophic in such chronic conditions as it was demonstrated in a study in China, where 77.7% of affected families were found to be debt [13]. One possible solution is to achieve universal health coverage, which is the goal of WHO by 2030. The reality, expressed in the 2017 Global Monitoring Report, is that "at least half of the world's population still lacks access to essential health services" and almost 100 million people globally are pushed into extreme poverty each year because of out-of-pocket health expenses [14].

2. Epidemiology-based planning of services: Accurate epidemiological data must be the basis of rational planning of services. Simple questions, such as how many patients with haemoglobin disorders do we have, and how are they distributed across the country, will determine where and how many dedicated centres may be needed. How many reference centres and how these should network with secondary centres is another issue that only epidemiology can answer. If the aim is to provide equal access to effective management then service development can only be based on such facts. Moreover, it should be known whether the number of existing patients is likely to alter over time. In hereditary diseases like the haemoglobin disorders changes will be influenced by the heterozygote population and its marriage patterns. This is true of static populations but the influence of migrations and genetic drift must also be considered. This means epidemiological monitoring and reporting. Haphazard development is uneconomical and will not serve the purpose of equity of care. Epidemiology therefore is required to influence policy and planning, to 'translate' data into actions and interventions. It is from this that the term 'translational epidemiology' is derived [15]. The effective application of epidemiological knowledge however, depends on the accuracy of the data, and this is a major weakness in many countries. The number of patients can only be accurately known if national registries are kept and any changes are regularly monitored, updating the registry. In countries where services are poor, many children die before they are diagnosed and so numbers are underestimated. More often local, clinic based registries are kept in some centres

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and not in others, so national numbers are often 'estimates'. The complications and contribution to premature mortality are also unknown variables.

3. Availability of national policies for the control based on translational epidemiology National policies for the control of haemoglobin disorders, especially policies based on translational epidemiology, are lacking in most countries. Yet without a policy that offers the possibility of reducing birth incidence, and a policy for quality service development, services will be inadequate or ineffective and the objectives of equity and optical care, cannot possibly be achieved. In this respect, epidemiological facts come to support advocacy activities by patient support groups and in this TIF has a responsibility to train and build the capacity of its member associations, to understand and better express the needs of their patients and their families. Policy development is influenced, not only by stakeholder interest, but also by political and social forces, economics, cultural considerations and what are perceived as priorities by current health authorities.

4. Knowledge on prevention and management: All stakeholders involved with haemoglobinopathy patients, professionals, as well as families and the patients themselves, should know the aspects of prevention and management that can result in the best possible outcomes. These elements of holistic management are the results of ongoing research by academic researchers, which indicate the practices that will achieve the desired outcomes. They are published as international guidelines [16, 17], or as national standards, which adapt the guidelines according to national conditions and policies [18, 19]. The aim is to assist the treating physician by providing decision support aiming to improve the quality of healthcare and to increase patient safety. Optimal, guideline based management has been shown to improve survival [20, 21], but also the quality of life of patients [22]. The availability clinical practice guidelines has been upheld as an essential part of quality medicine for decades [23, 24] and it is a priority for thalassaemia centres. Many centres complain that optimal care as expressed in TIF guidelines is difficult to follow in economically underprivileged societies. However, this is the reason why associations and federations of associations have been created – to advocate and persuade authorities to aim for the best possible outcomes.

5. Good quality laboratory support: Another service, essential for accurate diagnosis and for monitoring patients is good laboratory support. TIF and other guidelines clearly state the need for diagnostic workup before the first transfusion and they provide a timetable and a list of parameters required for patient monitoring throughout their life [16, 19]. Such parameters determine treatment decisions and must therefore be followed. Yet thousands of patients are treated according to a Hb and ferritin check performed at irregular intervals. Proper monitoring will give early warning of complications and has allowed lifesaving interventions [25]. Quality standards for laboratory tests for Haemoglobin disorders have been published [26]. Universal standards for specialised tests such as Magnetic resonance imaging for the quantitation of iron load are still pending in many parts of the world.

6. Continuity of care: Continuity of care from professionals who are experienced in thalassaemia care is still a problem because of staff rotations and inadequate staff training. Expert case management eludes many patients in countries, rich and poor. Professional expertise depends not just on academic qualifications but also on the number of patients treated over the years, adherence to guidelines and good clinical practice. Involvement in research is an added advantage. Networking with other specialists in the field is a major advantage since sharing experiences is one way to assist problem solving in a clinical setting [27]. Networking is also of particular importance in multi-organ conditions such as thalassaemia and sickle cell disease [3, 5, 16]. Networking is also best facilitated when electronic means are available, since the whole and lifelong picture of each patient can be shared between members of the treatment team.

7. Electronic health records: Electronic health records in the modern world are gaining ground and are most certainly of great importance in lifelong disorders, in which current status can be influenced by past events. Universal adoption of electronic records has yet to be achieved even in developed economically countries. Various barriers are encountered, such as user resistance, variations in local needs, interoperability with existing systems (this is particularly so when disease specific programmes are introduced as additions), system maintenance, governance and others. The need to network in both clinical practice and research, also brings technical issues, like interoperability, to the forefront, as well as issues of data protection and confidentiality. None of these issues are, however, insurmountable obstacles and when the benefits of information technology *versus* piles of paper records, are realised then the electronic health record is realised as a necessity. Such a system allows a true picture of trends over time and a true clinical picture of individual patients or groups of patients, and especially the outcomes.

8. Patient participation in care, service provision and research: Patient input in all aspects of care, service provision and research is essential. Much has been written about the 'partnership' *versus* the 'paternalistic' approach to patient care, its effect on adherence to treatment, self-management and the overall psychological health of the patient, especially where chronic diseases are concerned [28, 29 30, 31]. Basic to partnership is the doctor/patient relationship but none of this can be achieved without patients being well informed on their condition and its management. Patient information is a duty of the treating physician and his team. Patient education has been a principal advocated by TIF from its foundation as evidenced by its publications [32], the online patient educational platform (launched 2017) and its regional and international conferences which are designed for patient involvement. Patients cannot be passive recipients of treatment but active participants in interventions that affect their everyday life and their survival.

Availability and Quality of holistic services is the central concept of the elements described above. Quality assessment for the purpose of accreditation, involves much more and TIF has embarked on a programme that seeks to recognise and accredit centres of excellence for haemoglobin disorders, which is hoped to encourage more centres to reach a level of patient-centred care that will achieve outcomes that are expected, according to the achievements of medical science in the 21st century, and keep up with progress and new developments.

As a patient driven organisation, TIF has been monitoring patient concerns and has been encouraging them to voice these concerns during conferences as well as to their national health authorities. Examples of these concerns taken from patient quotes, are listed in Table 1.

From reports and from local visits, experts are aware that many elements of optimal care are missing in many centres. Examples include the non-existence of guidelines or standards for patient care and adherence to them is poor, outcomes such as survival rates, complication rates are not recorded and in general the average age of patients reflects poor results, adherence to treatment is poor, social achievements (education, marriage, employment, integration) are often also poor reflecting lack psychosocial support. Out of pocket expenses are the rule in many countries [13, 14].

In order to estimate the level of services as perceived by patients, TIF has conducted a survey among thalassaemia patients globally. At the time of writing, not all the results were available but a preliminary report is presented here.

Methodology

Design

As mentioned earlier, to map the necessary services to constitute a holistic patient care and assess the extent to which these services are available at good quality level to patients across affected countries, we drew on the following 8 categories to formulate questions that could elicit patients' evaluations.

1. Free or affordable healthcare based on country income
2. Epidemiology-based planning of services
3. Availability of national policies for the control based on translational epidemiology
4. Knowledge on prevention and management
5. Good laboratory support
6. Continuity of care
7. Electronic health records
8. Patient participation in care, service provision and research:

The questionnaire was directed to patients and families of patients with thalassaemia of various varying severity forms including multi-transfused beta thalassaemia patients (name the forms included in questionnaire).

The questionnaire was distributed online via the Survey monkey software and supplemented by hard copies for patients who did not have access to internet connection.

Analysis

The Human Development Index (HDI) was chosen as a valuable resource in the analysis of the data and interpretation of results and relevant to the purposes of this research to highlight the relationship between the level and quality healthcare services for thalassaemia patients, and promote policies and healthcare systems for amendment.

The Human Development Index (HDI) is a summary measure of average achievement in key dimensions of human development: a long and healthy life, being knowledgeable and have a decent standard of living. The HDI is the geometric mean of normalized indices for each of the three dimensions. The Human Development Index (HDI) was created by the United Nations Development Programme (UNDP) to emphasize that people and their capabilities should be the ultimate criteria for assessing the development of a country, not economic growth alone. The HDI can also be used to question national policy choices, asking how two countries with the same level of GNI per capita can end up with different human development outcomes. These contrasts can stimulate debate about government policy priorities. In this preliminary report, a total of 106 online responses were analysed. The majority of responses were from adult university graduates, which means that whichever country they come from, they were the best examples of the patient population, not reflecting the total population of patients especially in the countries which have not achieved a very high Human Development Index (HDI) [33].

The average age of this patient group was 29.8 years (range 2 to 57 years). Those over 20 who responded to questions relevant to adults, had an average age of 34.2 years.

Results

Demographics

The 106 respondents were from 33 countries:

Who region		Number of patients
Europe	11 countries	24 patients
East Mediterranean	5 countries	17 patients
South East Asia	7 countries	35 patients
West Pacific	4 countries	7 patients
Americas	4 countries	21 patients
Afro	2 countries	2 patients
TOTAL	33 countries	106 patients

These countries were classified according to the Human Development Index (HDI) and the responses were classified according to the HDI of the country of residence of the patient.

Seven indicators were chosen for this preliminary study to establish patients' view of the quality of services:

1. The pre-transfusion haemoglobin level at which they are transfused
2. The pre-transfusion haemoglobin, in relation to the delays in blood supplies
3. The out-of-pocket expenses for the provision of essential treatment
4. The frequency of MRI T2* estimation of iron load in the heart
5. The marital status of adult patients
6. The employment status of qualified patients
7. Patients' confidence in the correctness of their treatment.

1. Pre-transfusion haemoglobin should be, according to agreed guidelines [16], 9-10.5g/dl. In the responses to this survey, those that receive blood transfusions according to the guidelines are mostly form very high HDI countries, as shown in Figure 1. While those transfused at Hb levels below 9g/dl are from high and medium to low HDI countries.
2. The presence of delays in providing blood at the right time for each patient in order to maintain a good level of Hb, reflect the level of efficiency and effectiveness of blood donation drives, but it is also an indirect indicator of the quality of the blood transfusion services of a country and the community involvement. Again, our results demonstrate that it is patients in medium/low HDI countries who experience delays and so have to live with lower Hb levels (with all the consequences of poor oxygenation and extramedullary erythropoiesis). Figure 2.
3. Sustained provision of care is impossible for many families

Table 1. Patient comments on services that they want.

• "Medical & nursing staff that I can trust"
• Good communication: given TIME and staff that LISTENS
• Consideration for the patients' needs for a normal life (clinic times, waiting time): fitting treatment around the patients' life and not administration needs.
• Given treatment options to discuss – the partnership model
• Knowing that protocols and standards of care are followed
• Patient involvement in planning services & setting standards
• Ensuring that patient reported outcomes are recorded and considered

due to the high out-of-pocket expenses required. Patients' responses to our survey indicate that full state coverage is available to less than half of the patients around the world who answered our questionnaire (48.7%). The degree of coverage by various insurance schemes was not made clear, but it is felt that it is not likely that all aspects of chronic care is covered. This goes to suggest that half of thalassaemia patients require family assistance to maintain optimal care. Figure 3.

4. Patients are recommended to have an MRI test for cardiac iron on an annual basis. In this survey, 60% of patients from medium/low HDI countries have never had this test and this includes over a third of patients from high HDI countries. Figure 4.
5. Marital status reflects more than the patients' health, but also several social and cultural issues (such as prejudice), in which economic factors may play a minor role. In patients over 20 years old, in this patient population the cultural background was considered: Table 2.
6. The employment status of the patient respondents in this survey reflects their characteristics since most were educated and university graduates. In several countries, factors such employer prejudice, economic factors but also the family's and patients' view of the ability to work may play a significant role. Figure 5 shows that for qualified adult thalassaemia patients, the HDI status of the country does not significantly affect the chances of employment and a significant number of patients across the globe stay away from useful employment by choice.
7. Patients' confidence in the correctness of their treatment can be taken as indicator of the sufficiency and quality of communi-

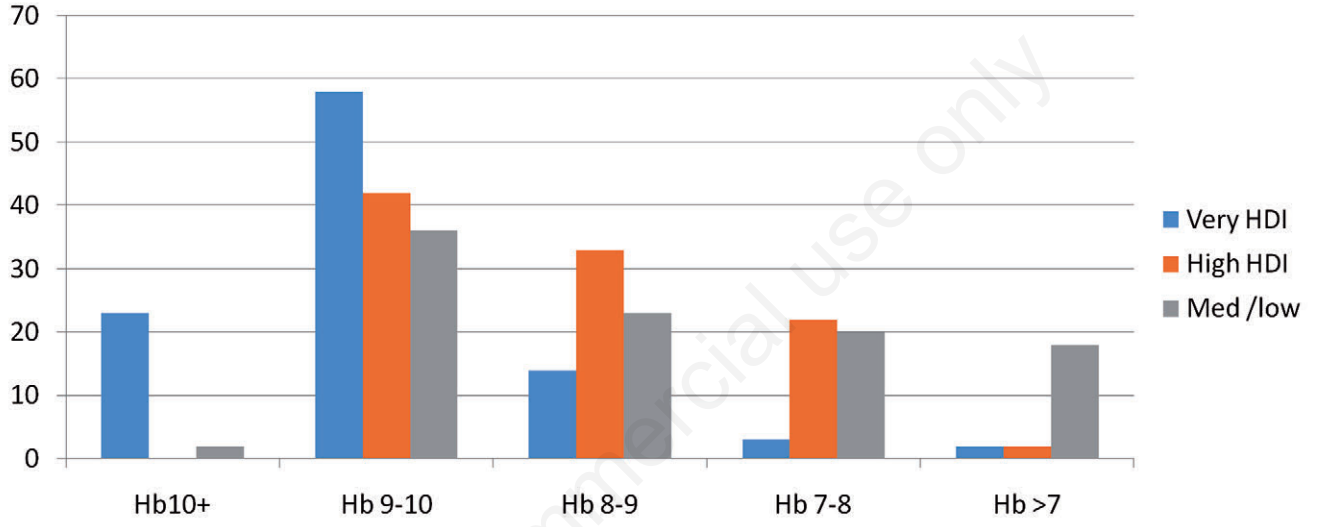

Figure 1. Pre-transfusion haemoglobin levels according to country HDI level.

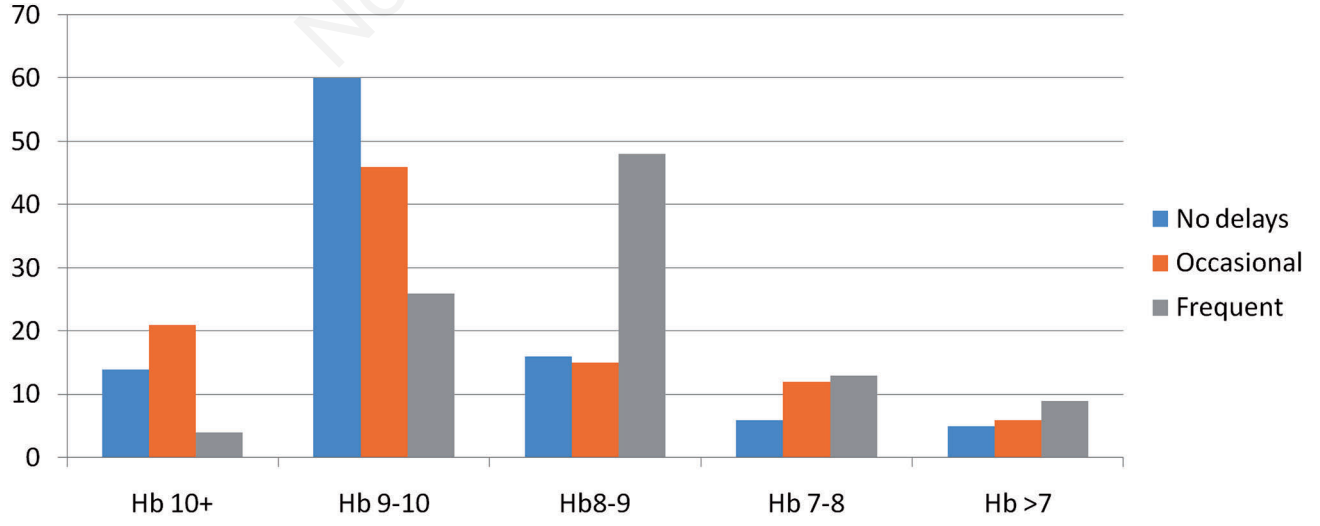

Figure 2. Classification of delays with respect to country HDI.

cation between patients and their treating physicians, a key service of healthcare directly related to patient's right to information (Figure 6).
- 47% are uncertain about the correctness (half of these are sure that treatment is not correct).
- Patients from all centres gave similar responses.
- Similar responses in a European survey 2014.

Discussion and Conclusions

To assess patients' views several more indicators have been introduced into the questionnaire, but were not assessed in this preliminary analysis, which is inevitably limited (The questionnaire can be viewed at its entirety at https://goo.gl/vNkxud). Not least, the data reported herein are patient reported outcomes, which essentially reflect their expectations as well as the factors that they perceive affect their quality of life. Other questions that are included are clinic working hours, transfusion timetables, days lost from work and school due to treatment and many others which can affect patient satisfaction. This paper is intended as an introduction to a more extensive study, but also a general indicator of issues affecting quality of care. The patients' view is very rarely studied and published. In this survey, the common denominator is a patients group of the same diagnostic category even though from many different backgrounds. Comparisons in such a heterogeneous group can only be made if they are categorised into groups with similar characteristics and the common denominator chosen in this case is the Human Development Index.

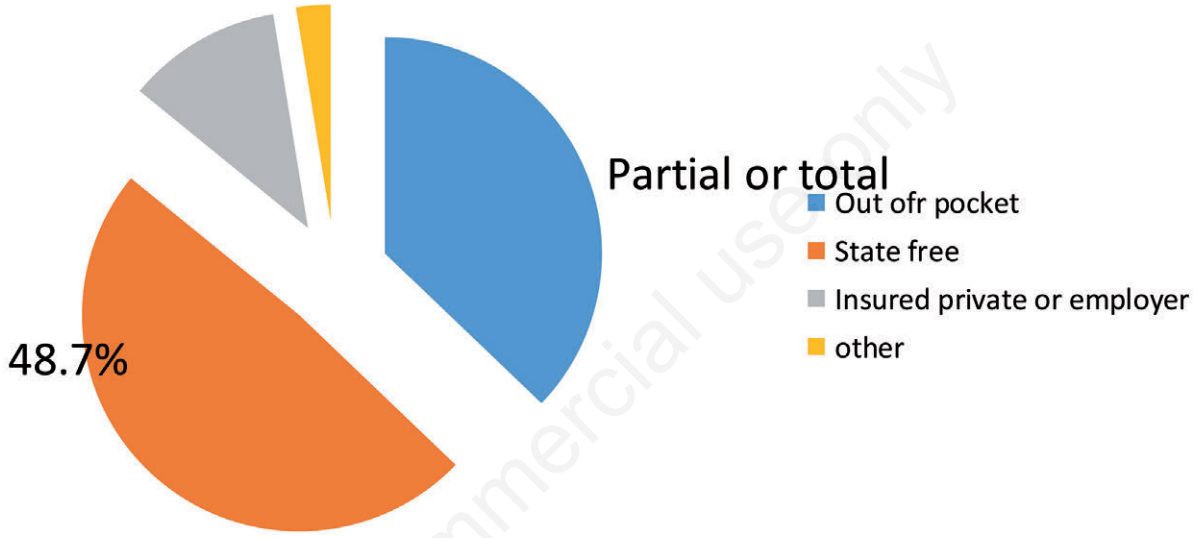

Figure 3. Availability of partial or total healthcare coverage according to country HDI classification.

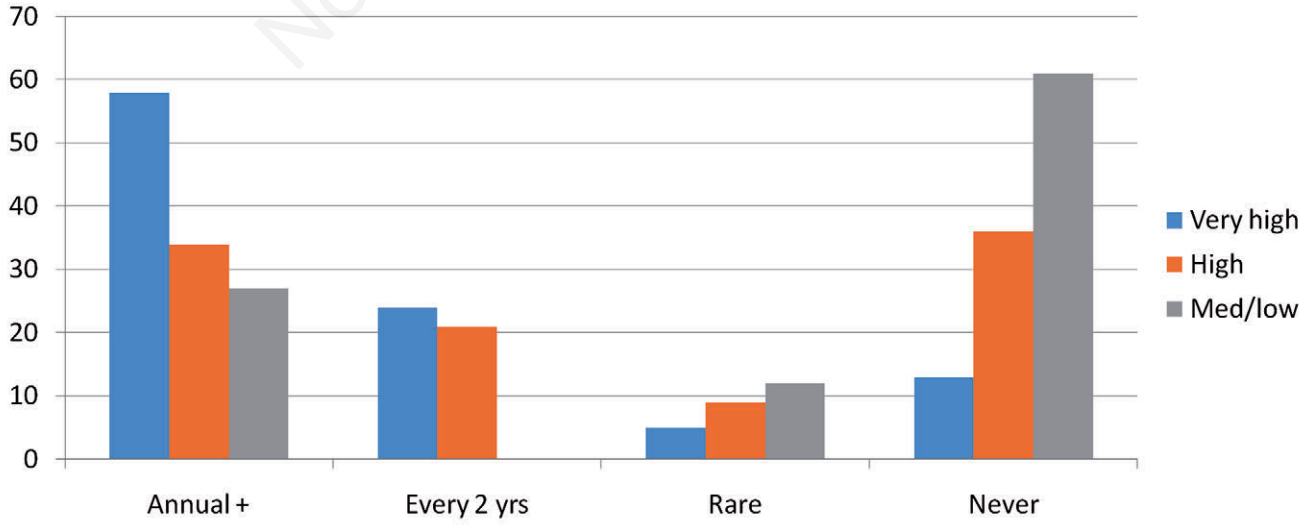

Figure 4. Frequency of MRI testing for cardiac iron and country HDI classification.

The main weakness of this survey is the small sample size made availablefor each HDI category; nevertheless, certain interesting conclusions can be drawn:

- Concerning pre-transfusion Hb level, it is noteworthy that around 15% of patients living and being treated in very high HDI countries state they are receiving transfusions below the recommended range. The reasons cannot be discerned from this study, and there may be acceptable clinical reasons. However, ignorance of guidelines and patient non- compliance in some centres may be factors and a more in-depth analysis is needed. The fact that 60% to 65% of patients in high, medium and low HDI countries are transfused below recommended levels is not surprising but it does signal a need for more vigorous professional education, advocacy for policy changes and patient education.
- Frequent delays in providing blood, a reflection on the blood banking system and the donation campaigns is again a characteristic more of low-income countries. This is not surprising, since according to the WHO, the highest percentage of blood donations take place in HDI countries. For example, the European WHO region, inhabited by 11% of the global population [34] and home to only 3.3% of the world's known thalassaemia population [35], reported 30% of the global blood donations.
- Behind much of the suffering and poor service provision in many countries is the lack of policies to support patients and their families, enabling them to provide even basic elements of management. Even blood and essential drugs have to be paid for and in chronic diseases, this leads to catastrophic results and early loss of patients. This is a major global issue in the WHO's sustainable development goals [36]. Unless governments and policy makers resolve this issue, thalassaemia patients will continue to miss the kind of treatment that can guarantee a prolonged life span that so many other patients are enjoying, even within the same country. Employment and marriage are aspects of life that are the results of many factors medical and social factors, but again inequalities are evident even in developed economies.
- One major issue is the professional-patient relationship. In this preliminary paper only one issue was discussed, that of trust in the treatment that is provided. In this aspect, the results from this survey were compared to a similar survey conducted by TIF within a project called ENERCA in 2012-14, in which the participants were European patients [37]. The results are very similar in that only 57% of the total patients asked felt that their treatment was correct while the rest were unsure. This issue of patient trust to their treating physicians' choices in their treatment, along with poor adherence to guidelines by centres and limited financial support seem to be the most serious contributors to poor outcomes.

It is important to note that, this survey represents patients' perceptions regarding the treatment they receive, a perspective seldom reported in the literature on haemoglobinopathies and one that merits more careful and more frequent evaluation. . It would be useful to correlate and contrast these results with input from professionals in these countries to enhance the validity of our conclusions.

Table 2. Marital status of thalassaemia patients across cultures.

Cultural group	Married patients	Single	Cohabiting	Divorced
Western culture	48%	34%	13%	5%
Arab culture	35%	60%	1 case	0
Asian populations	20%	78%	0	2%

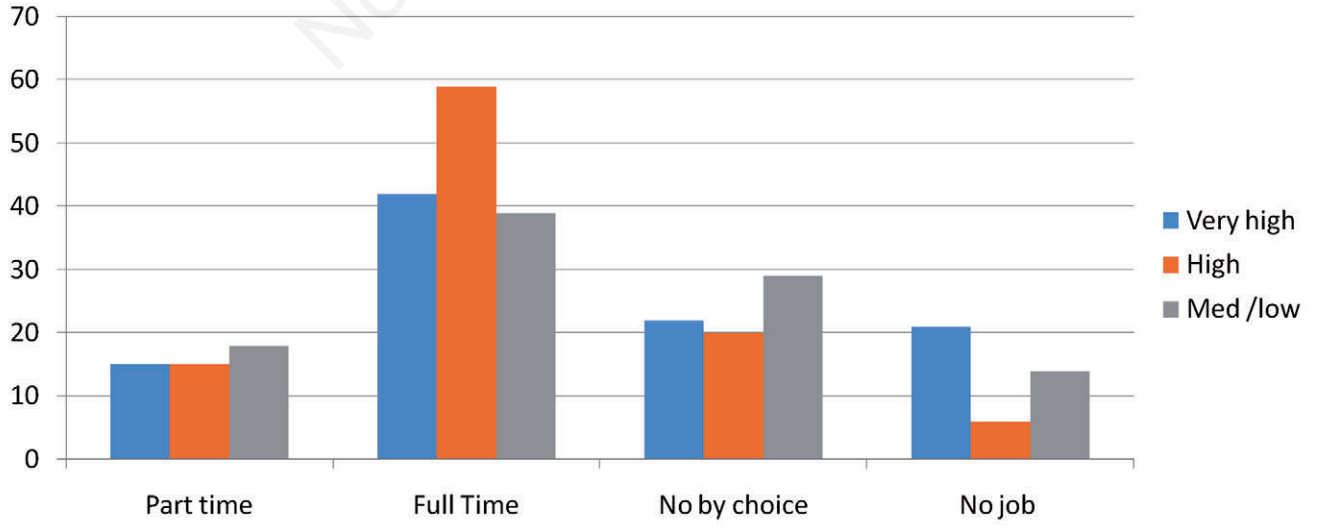

Figure 5. Employment status of thalassaemia patients according to country HDI classification.

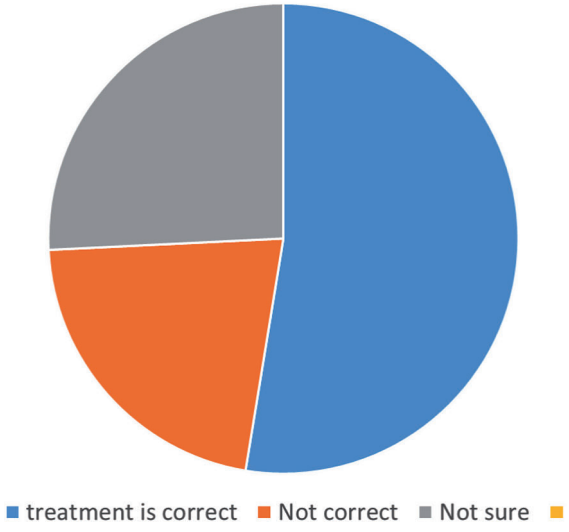

Figure 6.

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Global initiatives for improving quality healthcare by the Thalassaemia International Federation

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In today's health care arena, a number of issues are being raised that have received more attention either from the health care consumers or the media. The 1990s can easily be dubbed the period of "performance measurement". Whether as a provider, a consumer or a purchaser, each was looking for ways to satisfy the other through measuring and reporting on care outcomes. Accountability was at stake in that period. Several third-party organizations attempted to produce certain measure to report on these care outcomes. A number of "indicators" were developed and measured and "report cards" were assembled.

All of these activities were done in the effort to measure performance. WHO organized and facilitated a number of activities related to quality assessment, performance improvement and outcome measurement. A large number of countries and institutions participated in these activities and initiatives. And at the end, all agreed there had to be an organized mechanism to account for quality, continuous measurement and improved performance in health care organizations. In order to do this, a mechanism for certification, licensure or accreditation should be put in place.

This trend continued in the 2000's and until now where performance measurements and improvement as on the top of the agenda of any healthcare organization and country healthcare system. Related to performance is accountability. In particular professional accountability both at the individual and the institutional levels became extremely important when dealing with issues related to performance.

Certification and licensure

It is very easy for a layperson to get confused with the terms and mechanisms of certification, licensure and accreditation. In general, certification, licensure and accreditation are all methods of evaluation and are also methods of assessing and rewarding organizations (and individuals) for healthcare quality. Accreditation is the only method however that requires a health care organization to comply with a rigorous set of performance standards and be subjected to a comprehensive process of self-assessment in addition to external evaluation. Both licensure and certification follow the same principle of assessment whereby an organization must demonstrate to the granting agency its capability and proof that it has met the standards prescribed by that granting agency, at least at the minimum levels. The difference between the three is therefore based on the rigor of the assessment process and whether the evaluation is comprehensive to all aspects of the organization. It is believed that in the case of accreditation, the process and the standards are more rigorous and more comprehensive in nature.

Therefore, certification can be defined as a process of assessing the degree by which a facility, product, unit or professional attains minimum standards. It is specific to the nature of the assessment, and the entity is "certified" as a special agency for the purpose of providing a specific service or activity.

Licensure is somewhat more similar to certification than accreditation. Again it is targeted at all entities, individuals, organizations or groups. Licensure can therefore be similarly defined as the process of assessing the extent that a facility, organization, or professional has attained minimum requirements. Unlike certification, however, without a license, an entity is prohibited from practicing the activity for which a license is needed. Therefore licensure is usually a government-sponsored activity that is put in place to control the practice of a profession or an act that has the potential of risk to the recipient or the beneficiary.

What is accreditation?

Accreditation is a rigorous and comprehensive evaluation process through which an external accrediting body assesses the quality of the key systems and processes that make up a health care organization and is applied primarily to organizations rather than individuals, departments or units.

Accreditation was developed in response to the need for standardized, objective information about the quality of health care organizations. Organizations seek accreditation for different reasons but most do so in an effort to increase market share and to win customer satisfaction and professional reputation.

The International Society of Quality in Health Care (1998) defines accreditation as: "…self-assessment and external peer review process used by health care organizations to accurately assess their level of performance in relation to established standards and to implement ways to continuously improve the health care system. Quality standards and the external peer review process are directed by nationally recognized autonomous, independent accrediting agencies with a commitment to improve the quality of health care for the public".

Why accreditation?

For more than four decades, accreditation has been the highest form of public recognition a health care organization could receive for the quality of care it provides. Accreditation offers quantitative as well as intangible benefits to a health care organi-

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zation besides public recognition. Accreditation can actually enhance the organization's strategic management decision-making process (AAAHC, 2013).

The purpose of accreditation can be summarized into the following categories:

1. Demand of the customer
2. A forum for measuring performance
3. Standardization and variance control
4. Benchmarking
5. Report cards
6. Quality improvement
7. Positive competition
8. Reward and recognition
9. Efficiency
10. Effectiveness

The above reasons are making accreditation an important process to adopt by a country and by organizations to seek:

Health care consumers are becoming increasingly aware of the different requirements a health care organization must meet in order to be considered a quality organization. They are also becoming interested in learning about the status of care provided by an organization judged by its peers or professional experts.

Accreditation provides just the answers and the assurances that health consumers are asking for. Accreditation provides for a mechanism for an objective unbiased peer review of a health organization. It provides the consumer a set of measures by which they can judge a health care organization in comparison with similar organizations.

Accreditation standards are developed to be as quantifiable as possible. Each standard is further stated in the form that will allow its measurement. Such measurable forms of the standards are often called indicators or depending on the accrediting organization may be referred to as measurable elements, evidences of performance or the like.

These standards follow the various functions and units health care organizations perform and possess. Standards are developed and are updated annually by a group of experts that are related directly to the process of care and to the structure of services rendered by the health care organization.

Compliance with these standards is a proxy measure of the performance of such an organization. Of course compliance may have to be substantial for the health care organization to receive the seal of approval from the accrediting organization. In this way accreditation can work as a measure of the performance of the organization, especially in such areas as structure and process.

One of the main activities of accreditation is to set standards that a health care organization must meet. Experts usually rigorously develop these standards. It is with these standards that the accreditation agency is able to measure the quality of the health care organization they want to evaluate for accreditation. Therefore, these standards soon become the yardsticks by which performance is measured and accreditation is achieved. Standardization is important in order that objectivity can be assured in the evaluation process. It is also a mechanism for controlling outcomes and comparing performances.

Meeting certain standards will render the health care organization "accreditable" and will decrease variation between its current performance and the desired one. Standardization is also useful in controlling cost by controlling expectations, predicting outcomes and facilitating effective budgeting.

Benchmarking and report card capabilities are two of the reasons why health care organizations should seek accreditation. These are also reasons why accreditation should be developed in order for organizations to be compared with one another based on the findings of accreditation.

Benchmarking is a process of identifying the best process, activity or outcome and to find ways to study them and emulate them in one's own setting. Through the process of accreditation, health care organizations are encouraged to look for the best processes of other organizations in order to study these processes and learn about performing them so that they can be imported and implemented in that organization.

Benchmarking is usually enhanced by the fact that most quality organizations are accredited. Similarly, one of the reasons for accreditation is to list on the health care organization's report card (outcome measures) that they are accredited. A report card is a document or report that shows a list of performance measures of that organization used primarily for positive marketing (self-generated and designed report cards) or for comparing organizations between one another using a set of measures that common to all (regulator-induced report cards).

Health Care organizations that do not have accreditation listed on their report cards do not show complete and certainly not credible report cards. Therefore, organizations must seek accreditation and attain it in order for them to list it on their report card both for marketing and comparison objectives.

According to the quality improvement cycle shown below, accreditation is involved in all of the steps of the cycle, including quality improvement. The process of accreditation emphasizes assessment but it also encourages improvement based on the outcome of such assessment. It also encourages organizations to initiate improvement projects.

Most of the new accreditation standards call for health care organizations to demonstrate their capabilities of identifying improvement opportunities and initiating processes for improvement and development. Accreditation agencies respond positively to those organizations that demonstrate their experience in "closing the loop" from the identification and analyses of improvement opportunities to selection and implementation of actual improvements and then maintaining and sustaining that improvement. Therefore, accreditation will stimulate improvement efforts in health care organizations and will bring these organizations to a higher level of accountability.

Accreditation provides a mechanism for comparison between health care organizations. Those organizations that have achieved accreditation, especially "commendation" or "excellent" status, will have a positive image and will use that distinction to market their services accordingly. Accreditation can therefore be used as a tool for positive marketing and as a tool that enhances positive competition between health care organizations. Competition can be based on price or other factors. Competition based on quality as exemplified by the attainment of accreditation is a form of non-price competition and is a form of positive competition. This type of accreditation is in contrast with the type of competition exhibited by and between political candidates where they each try to find weaknesses in each other performance or character to attack.

Components of accreditation

A typical system of accreditation (as seen below) is organized around four different components: administration, standards, communication and education, and surveying.

The board

Most accreditation agencies are organized as independent private entities (some with government mandate and other are actually governmental agencies) that are usually not-for-profit. Of course such a system must have credibility, and this is usually attained

through an upper management structure such as a board of directors or a governing board. Accreditation agencies are structured in such a way to provide market representation, credibility and authority. They are also organized for the purpose of enhancing performance of health care organizations in that country or internationally. To achieve this status, most agencies have a "supervisory" board of directors or board of trustees. This board is usually made up of a mix of healthcare professionals, health industry representatives and prominent community leaders. Therefore it will consist of representatives of all of the major players in the health care system including representatives from both the government and the private sector. Professional organizations and societies may also be included on such a board. As an example one accrediting agency in the US has on its board representatives of the American Hospital Association, The American Medical Association, the American College of Surgeons, and the American College of Physicians. Sometimes prominent leaders from the community may be asked to serve on an accreditation boards of directors that may not even have any link to health care to give such board a broad representation of the professional and lay communities.

Whoever the board members are, the roles and responsibilities of such a unit is to provide oversight of the activities of the accrediting organizations. Therefore they are responsible for setting the agency's strategy, approve its overall policies and procedures, its operational plans, and the appointment of the agency's top administrator or CEO. Of course the main function of this board besides the above is to confirm and manage the award of accreditation decision of the surveyed health care organization. Therefore this board is responsible for: • Evaluation of surveyors' recommendations • Verification of information provided by the survey process • The accreditation award decision • The appeal process • Re-evaluation and periodic surveys • Re-accreditation • Accreditation violations including suspensions and abrogation.

Administration

The accrediting organization will have an administration. This component will have a number of activities and functions that are supportive and somewhat facilitative in nature. This component is usually responsible for providing leadership and administrative to the accreditation process. Specific functions include: • Managing the day-to-day activities of the accrediting agency • Facilitating the application process • Collecting of the application and survey fees • Scheduling of the on-site survey • Identification and contact of surveyors • Travel arrangements of surveyors • Secretarial and clerical support. • Help desk/customer service, etc. • Responding to health organizations' inquiries and • Managing communications with external bodies and regulators.

Education and communication

The second component of the accrediting organization is education and communication. This component is primarily responsible for increasing awareness of the target organizations and their employees of the process and the standards of accreditation. Specifically, this component is responsible for: • Seminars/workshops • Conferences • Consultations and advice • Newsletters • Web-site • Direct mailings • News releases • Marketing.

Standards

The third component is related to the setting and continuously updating the accreditation standards and the scoring guidelines for measuring compliance to the standards. Specifically, this component will be responsible for: • Organizing the domains or chapters/sections for the standards manual • Developing and setting the accreditation standards and their measures • Identifying the documentation requirements for evaluating compliance • Establishing scoring guidelines • Organizing and updating the standards manuals in general.

Surveying

The fifth component of the accreditation organization is probably the most important; where the actual assessment of the health care organization is handled. Professionals working for this component will be responsible for: • Identification and Selection of surveyors • Training and orientation of surveyors • Teaming and scheduling of surveyors/facilities • The organizing of the site visit • Managing the survey report and the score card • Managing the surveyors' recommendations.

The accreditation core standards

Depending on the accrediting organization's emphasis, the areas for the development of standards may be different from one another. Also, the type of facility to be accredited has an effect on the type and the "domains" of standards to be developed by the accrediting organization. The following are three examples of standards chapters or domains for three different health care organizations; hospitals, ambulatory care organizations and health maintenance organizations.

What will be the structure of the TIF accreditation program?

TIF has a unique opportunity in helping its many members improve their performance and achieve international status. The accreditation program will meet this objective. The program could be housed at TIF as a separate program but under the same umbrella of TIF.

The program will have different components and functions and will serve as the accreditation "agency" for TIF member organizations seeking to enhance their performance and status among other similar organizations globally.

Similar to ISQua's International Accreditation Program, TIF's accreditation program will have a similar organizational structure and functions. The program however will have to have its own board, human resources and separate budget.

The main functions of the accreditation program

- Create and maintain the register of accredited organizations and the register of accreditation personnel;
- Represents TIF and will be participating in all relevant international, European and regional organization and meetings on accreditation;
- Draft and execute related international and national agreements on cooperation and mutual recognition of accreditation
- Seek, achieve and comply with international accreditation standards (*e.g.* ISQua) and become an accredited organization for the granting of accreditation of other organizations.
- Develop and deliver training of accreditation personnel and empower them to carry out accreditation activities according to the set requirements;
- Provide educational and awareness material to providers and the public on issues related to accreditation and the associated standards.
- Develop and regularly update the pertinent accreditation standards for the different member organizations globally.

- Assess compliance of member organizations to accreditation standards through periodic site visits and periodic as needed other surveys to sustain such conformity to the standards.
- Make decisions as to the degree of compliance of healthcare organizations to the accreditation standards and decide on the awards of accreditation to such facilities or the revocation of such awards for non-complying organizations
- Develop policies, procedure and related guidelines on the preparation for site visits and the delivery of such visits to healthcare organizations nation-wide
- Develop guidelines and train surveyors on the on-site survey methodology and procedures of conducting the site visits and scoring of the standards and on reporting of the findings.
- Assess and collect surveying fees and related financial requirements to operate and sustain an effective and objective national accreditation program
- Create technical accreditation committees and approval of their provisions;
- Provide a set of guidelines and policies on accreditation decisions appeals and grievance procedures.
- Organize and deliver seminars, webinars, workshops and training venues on the accreditation standards to healthcare professionals and their organizations
- Organize and administer an annual consensus international conference on accreditation process, standards and related outcomes
- Provide an international "help-line" and mechanism to provide logistical and expert support to member organizations as they prepare for their accreditation award
- Provide comparative information to select national regulatory agencies and the public on member organizations' performance and patient related outcomes
- Assist in enhancing global awareness on patient rights and safety and on providers' responsibilities and ethical behavior

A typical system of accreditation (Figure 1) is organized around four different components: administration, standards, communication and education, and surveying.

The board

Some of the board's functions are:

- Approval of accreditation related policies and procedures developed by the accrediting body as well all operational plans of the program and its strategic plan
- Provide oversight and overall supervision of all activities related to accreditation including the development of standards, the surveying the healthcare organizations and the education and training for healthcare professionals.
- Overseeing all budgetary and financial transactions affecting the accrediting body and their activities to collect fees and enhancing its financial stability
- Address any and all accreditation violations including suspensions and abrogation of accreditation.

The administration (operation unit)

Some of the functions include:

- Implement and maintain the overall accreditation program including all planning, financial and accounting activities.
- Manage all internal communication systems including IT, telephone, and website services of the accreditation program.
- Develop, control and regularly update management system documents including all internal policies and procedures and supportive documents for the operation of the accreditation program.
- Manage the scheduling of the on-site survey,
- Identify and contact of appropriate surveyors for the survey visit taking in consideration issues related to availability, logistics, and conflicts of interest
- Coordinate travel arrangements of surveyors and the processing of travel related expenses and reimbursements
- Provide relevant secretarial and clerical support to the accreditation staff, surveyors and sometimes to member organization as needed and seen appropriate.
- Maintain personnel files and the human resources management of accreditation organization/center

Awareness, education, and communication

This component may be responsible for:

- The organization and delivery of seminars/workshops on the accreditation standards including the development of curricula, the identification of the instructors/trainers, the development of the training material, the marketing and solicitation of the events as well as the selection and logistical support at the venues
- The organization and administration of accreditation related international conferences and gatherings
- The marketing and deliver of focused consultations and advice to interested healthcare organizations on issues related to accreditation, the standards and how to comply with them

Standards

This component may be responsible for;

- Organizing the domains or chapters/sections for the standards manual
- Developing and setting the accreditation standards and their measures

Surveying and external monitoring

The fifth component may be responsible for:

- Identification and Selection of potential surveyors recruited or nominated from different member organizations internationally.
- Training and orientation of candidate surveyors and the retraining of established and seasoned surveyors
- Managing the surveyors' recommendations including their distribution to the Board and later with healthcare organization
- Developing the national database for required performance measures and the publishing of periodic benchmarking, individualized and comparison reports for healthcare organizations

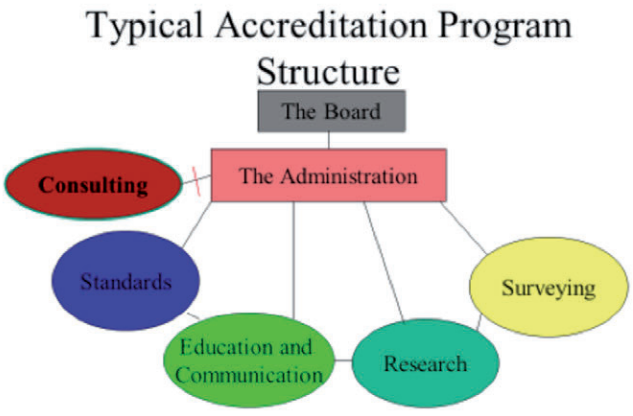

Figure 1.

Legal compliance and appeals

This unit may be responsible for:

- Provision of a Commission on Appeals by establishing main policies and procedures for consideration of appeals of against decisions, actions and inactions of the accreditation agency including its survey findings and accreditation decisions and commissioning specific actions regarding appeals
- Responsible for responding to any legal matters and law related issues and inquiries including any court related actions and proceedings that may arise and affect any of the staff of the accreditation organization during their official operation and duties.

Challenges of the TIF accreditation program

Although accreditation has many advantages as outlines earlier, there are some challenges that need to be addressed here.

1. Resources. Identifying new and suitable resources to start the program is the most challenging action. Not only new funds are needed but also identifying the right individuals to provide the support and sustainability needed for the program. There are expenses for consultants and expenses for documentation and related material development including standards, guidelines, policies and measures. Then there are expenses for training, marketing and winning buy-ins from member organizations for the program to sustain and succeed.
2. Buy-ins. Certainly, this issue is the most challenging. Trying to get members to first accept the program then subscribe to it and sustain it will not be that easy to achieve. Nevertheless, these challenges and similar others are achievable and will be fruitful in the long run. Patience on the part of TIF and its constituents is the key to achieve the objective of accountability.
3. Organization and administration. As mentioned earlier identifying the right personnel to advice, support and administer the program will not be that easy. Not every good professional is one that can help with accreditation. There is a need for highly qualified and trained individuals to establish and continue to sustain the program. Additionally, besides human resources, there is the need to develop all the material for the program from job descriptions, to standards, to surveyor guidelines, to training material to policies etc.
4. Time and results. This is a long process and will require many months to build the program at least on paper, then get the necessary approvals from TIF constituents, get buy-ins and subscribers, and then launch it globally.

Program participation

In order to make the program sustainable at least for the first few years of operation, the Accreditation program should become mandatory for TIF's member organizations. Existing organizations will be given up to 3 years to get accredited but should start preparing for it right away. For new programs, they should be given up to 18 months to achieve accreditation once they become operational. Mandatory accreditation will insure maximum participation and will help sustain the program. Bit more importantly it will put all member organizations at a similar level of performance and would share the same operational standards thus improving their processes and outcomes. Additionally, mandatory accreditation will generate the needed additional resources to sustain the program and make continuous improvement for TIF and its members.

The challenge is how can you make that decision and achieve full buy-ins and active participation from all members. With adequate marketing, strong messages, and getting the Board's support will all help achieve that goal. This decision will not be considered until the accreditation program is built and all required documentations are developed. Certainly a credible consultant will be instrumental is assisting TIF complete this task.

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Osteoporosis in thalassaemia

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Abstract

Osteoporosis is a prominent cause of morbidity in patients with thalassaemia major (TM) with a complex pathophysiology. Patients with TM and osteoporosis have elevated markers of bone resorption. This increased osteoclast activity seems to be at least partially due to an imbalance in the receptor–activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) system, which is of great importance for the regulation of osteoclast differentiation and function. Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of osteoclasts by RANKL. By blocking RANKL, denosumab inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass in postmenopausal women and patients with thalassaemia-induced osteoporosis.

Introduction

Osteoporosis is a prominent cause of morbidity in patients with thalassaemia major (TM) and has complex pathophysiology (1). Therefore, the necessity of understanding the underlying mechanisms for bone destruction in these patients seems to be compulsory.

Recent identification of novel markers of bone remodeling and osteoclast function has significantly contributed in understanding the pathophysiology of the disease.

Although osteoblast dysfunction is thought to-date to be the major pathogenetic mechanism for osteoporosis in TM, there is also evidence of increased osteoclast activation in these patients. Both Dresser Pollack et al (2000) (2) and our group have shown that patients with TM and osteoporosis have elevated markers of bone resorption, such as urinary levels of N-terminal crosslinking telopeptide of collagen type I (NTX), which is a specific marker of bone resorption, and increased serum levels of tartrate resistant acid phosphatase isoform 5b (TRACP-5b), an enzyme that is produced only by activated ostoclasts (3). The RANK/RANKL/OPG system seems to be of great importance for the activation and proliferation of osteoclast precursors. We and others have previously shown that RANKL, the most potent osteoclast activator, is elevated in the serum of TM patients and correlates with reduced bone mineral density (BMD) (3, 4). The increase of RANKL, followed by unmodified OPG levels, with the consequent increase of RANKL/OPG ratio may represent a major cause of uncoupling bone turnover observed in thalassaemia patients.

The increased bone resorption observed in TM patients with osteoporosis has led to the use of bisphosphonates (inhibitors of osteoclast function) in the management of osteoporosis in this cohort of patients (3, 5, 6). Both oral (alendronate) and intravenous (pamidronate, zoledronic acid) bisphosphonates have been used in TM patients with the intravenous ones to show the highest efficacy (1). However, a novel monoclonal antibody (denosumab) which targets RANKLis now available for osteoporosis patients and thus it is of great importance to know its efficacy in thalassaemia patients with osteoporosis.

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Mechanism of action of denosumab

Osteocyte is the key cell for starting bone remodeling. In cases of microcracks they release RANKL, which binds to RANK on osteoclasts and osteoclast precursors, activating osteoclasts that resorb the destroyed bone.

Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of mature osteoclasts by RANKL and prevents the maturation of osteoclast precursors and multinucleated osteoclasts (7).

It has a circulatory half-life of approximately 26 days, and like other monoclonal antibodies, the clearance of denosumab is through the reticuloendothelial system and does not depend on renal clearance. By blocking RANKL, denosumab inhibits osteoclast formation, function and survival, and thus it decreases bone resorption and increases bone mass and bone strength in both cortical and trabecular bone.

On the contrary, bisphosphonates do not inhibit osteoclast formation but they lead to their apoptosis through their binding into hydroxyapatite and their internalization by osteoclasts during the resorption process.

In addition, other biological inhibitors of the RANK/RANKL pathway, such as OPG linked to an immunoglobulin crystallizable fragment (OPG-Fc) and RANK linked to an immunoglobulin crystallizable fragment (Fc), were used to evaluate the pharmacodynamic properties of denosumab in rodent models. These studies show that denosumab is a potent inhibitor of bone resorption via inhibition of RANKL.

Clinical experience

Denosumab 60 mg every 6 months has been generally well tolerated in clinical studies. In FREEDOM study, there were no significant differences between subjects who received denosumab and those who received placebo over 36 months, in the total incidence of adverse events, serious adverse events, or discontinuation

of study treatment because of adverse events (8). Long term treatment, for up to 7 years, remained well tolerated and was associated with maintaining low incidence of clinical fractures. Denosumab has been licensed for the treatment of postmenopausal osteoporosis, as clinical data confirm that it leads to significant increases in BMD, with decreased risk of vertebral, hip and non-vertebral fractures. It has a very good renal safety profile in contrast to 3rd generation BPs (*i.e.* zoledronic acid), which need dose modifications according to CrCl.

The effects of denosumab on TM- induced osteoporosis

However, there are no prospective data for the effects of denosumab on TM- induced osteoporosis. Our center, evaluated the efficacy of denosumab in patients with thalassemia and osteoporosis in a randomized, placebo-controlled, double blind, single-site, phase 2b clinical trial.

The primary objective of this study was to evaluate the results of denosumab on lumbar spine (L1-L4) BMD in patients with TM and osteoporosis as compared to placebo at 12 months, while secondary endpoints included the evaluation of the effects of denosumab on femoral neck (FN) and wrist (WR) bone mineral density (BMD) at 12 months, the evaluation of the safety profile of denosumab as well as its effects on bone turnover markers. The main inclusion criteria included: adult patients (>30 years of age) with TM and BMD T-score between -2.5 and -4.0 in at least one of the examined sites (L1- L4, FN, WR). The main exclusion criteria included: impaired renal function (eGFR of ≤30 mL/min), elevated ALT and/or AST >2 fold the upper limit of normal (UNL), heart failure (NYHA above 2), administration of bisphosphonates within one year of study enrolment and the presence of any other disorder that affects bone metabolism. Patients were assigned into two treatment groups: in group A, 60 mg Denosumab was administered sc, every 6 months for 12 months for a total of 2 doses (day 0 and day 180); in group B, placebo was administered sc, at the same time. All patients received calcium and vitamin D supplementation. Measurement of BMD with dual energy X-ray absorptiometry at three body sites (L1-L4, FN, WR) was performed during the screening period and at the end of the study. The following biochemical markers were evaluated on the day 0 and then every 3 months up to 12 months (every patient had 5 measurements): i) osteoclast regulators: sRANKL and osteoprotegerin (OPG); ii) osteoblast inhibitors dickkopf-1 (Dkk-1) and sclerostin (SOST); iii) bone resorption markers: C-telopeptide of collagen type-I (CTX) and TRACP-5b; and iv) bone formation markers: bone-specific alkaline phosphatase (bALP) and osteocalcin.

Patients of group A (denosumab arm) achieved an increase in both L1-L4 BMD ($p<0.001$) and FN BMD ($p=0.022$), while there were no changes in WR BMD. Patients of group B (placebo arm) achieved a slight increase in their L1-L4 BMD and a significant decrease in their WR BMD ($p=0.008$). The percentage increase of L1-L4 BMD was higher in denosumab arm than in placebo arm (6.02±5.30% *vs* 3.11±5.46%, respectively; $p=0.03$), while the advantage of denosumab regarding WR BMD was much higher compared to placebo (-0.22±5.40% *vs* -4.15±8.58%, respectively; $p=0.02$). No grade 3 or 4 toxicity was observed in this study. Patients who received denosumab showed a dramatic reduction of sRANKL, sRANKL/OPG ratio, CTX, TRACP-5b, bALP between baseline and 12th month ($p<0.01$ for all comparisons) without changes in Dkk-1, SOST and OC. On the contrary, placebo patients showed an increase in sRANKL, OPG, Dkk-1, CTX, TRACP-5b, bALP during the study period ($p<0.01$ for all comparisons) along with a slight increase of SOST and OC (p=NS).

In conclusion, denosumab, given twice per year in TM patients with osteoporosis, increases the BMD of the L1-L4 more efficiently than placebo after 12 months, with excellent safety profile. Denosumab also reduced markers of bone resorption and osteoclast activation without affecting Dkk-1, which was increased in placebo arm patients in whom there was a significant increase in osteoclast activators and both bone resorption markers. These data support the use of denosumab for the management of TM-induced osteoporosis. However, studies with larger number of patient with thalassaemia induced osteoporosis are needed for evaluating the efficacy and long-term safety in these patients.

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The role of the clinical nurse specialist in haemoglobinopathies

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The role of the Clinical Nurse Specialist (CNS) is an ever-developing role that is integral in the care of individuals with haemoglobinopathies.

Haemoglobinopathies are complex disorders that require specialist knowledge to deliver the very best care. In order to offer the best possible patient centred care, the CNS is required to be a constant member of the team, who practises at the highest standard and promotes independence and the expert patient. The CNS supports and challenges patients and members of the multi-disciplinary team to ensure the best possible outcome.

This talk highlights the importance of the CNS role and the vital aspects of the role that a CNS should adopt, develop and improve upon.

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Quality of life: Transfusion dependent thalassemia *vs* non-transfusion dependent thalassemia

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Background

Although the improvements in the treatment and management of thalassemia patients in new years lead to the improved survival and quality of life (QOL) in this group of patients, QOL is still is an important dimension of care in thalassemic patients (1). WHO defines QOL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (2). Thalassemia is a chronic disease needs life-long care with multiple physical, mental and social complications that affect QOL in patients. The most important factors which affect QOL in thalassemia are: effects of the disease on family, skeletal and face changes, frequent blood transfusion and drug infusion, sexual impairment and infertility, heart and liver disease as well as endocrine disorders, anxiety and low life expectancy (3).

Discussion

Although thalassemia major (TM) is a life-long transfusion dependent, thalassemia intermedia (TI) is a milder form of the disease and may be non-transfusion dependent. QOL was evaluated frequently in TM (4-8) but its situation in TI and compare to TM is not well evaluated. In the first report by pakbaz *et al.*, 29 transfusion dependent TM and 19 transfusion independent TI patients were evaluated for QOL by Dartmouth Care Cooperative Chart System (COOP) questionnaire in children (mean age of 12 years old for TI and 17 years old for TM). Overall they found that QOL is more impaired in non-transfusion dependent patients compared to transfusion dependent (9). Also, Musallam *et al.*, compared QOL in adult patients with non-transfusion dependent (32 TI, median age 24 years old) and transfusion dependent (48 TM, median age 23 years old) thalassemia patients by the RAND SF-36 survey (10). In agreement with the previous study, they also found overall health-related QOL impaired in TI patients compared to TM patients. In the study by Musallam *et al.*, both physical and mental health score was significantly lower in TI patients compared to TM patients (10). The limitation of these two studies was a low number of the study population. In a recent study, we also evaluated the QOL in a larger TI study group (118 TI, 26.5±6.5 years old) and compared with 101 TM (19.5±4.4 years old) patients by SF36 questionnaire (11). Physical functioning was the best QOL score in TI patients in this study. In compare between TI and TM patients the total score was similar (66.5±15.4 for TI and 67.8±16.1) and based on subscales score, only physical functioning showed a better condition in TM compared to TI (86.9±12.9 for TM and 76.8±26.6 for TI, P<0.0001) (11). Although in this study unlike the previous studies health-related QOL in TI was not impaired compared to TM it was not also better as expectations. An Intercontinental Collaborative Study was conducted on 38 non transfusion dependent thalassemia (NTDT) and 97 transfusion dependent thalassemia (TDT) patients. All patients were over 18 years old from Canada, Iran and Lebanon. This study showed QOL of NTDT is better than TDT patients at younger age, but, while NTDT patients may not require regular transfusions based on conventional criteria, they may experience significant reduction in QOL especially at older ages. It seems long-term NTDT complications may contribute to find QOL is not better than TM at older age (12).

Conclusions

Thalassemia leading to reduce health related-QOL in affecting patients including physical, mental and social capabilities. As expected based on the studies, the QOL in non-transfusion dependent thalassemia is not better that transfusion dependent patients. Improving QOL and life expectancy in a chronic disease like thalassemia is the most important management approach in these groups of patients. Thalassemia centers and clinics should evaluate QOL in patients especially in non-transfusion dependent patients to determine best management modalities and improve QOL. Early and precise diagnosis, routine monitoring, parents and patient's education, financial support as well as enhancement in mental and psychosocial conditions are essential for improving QOL in thalassemic patients.

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Let's talk about thal: How communication can improve quality of life

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In many parts of the world, research, improved technology, and better medicine have enabled people with thalassemia to live longer. It is tragic that due to global disparity in healthcare, in areas of the world where thalassemia is most prevalent, the mortality rates are high, and often, patients do not survive past adolescence.

Each stage of life holds different challenges for people with thalassemia, and if patients are fortunate enough to reach adulthood, then they are faced with a new set of challenges uncommon to pediatric patients. Providers who have dedicated their careers to improving care now must work toward helping patients achieve a high quality of adult life by addressing such struggles. However, there is one topic that affects patients and providers universally at every stage of life—implementation of the concept can be easy, and it is free: that is COMMUNICATION!

I am a 45-year-old thalassemia patient. I have 17 years of experience working in thalassemia outreach and advocacy at a children's hospital, I am currently a thalassemia program consultant at Children's Hospital Los Angeles, and I follow topics related to thalassemia on over 60 social media sites. Consequently, I have become more aware of patient needs, challenges, and obstacles on a global level. My thought process for this presentation led to a goal of discussing quality of life in a way that considered patients all over the world, not just the United States. The common factor that can improve quality of life for patients around the globe is a high level of communication.

Communication can begin upon diagnosis. Though communication is vital to surviving with thalassemia and a key to quality of life, it is a challenge for many people, and at times, a curse. People do not want to talk about thalassemia, and often, they go into hiding. What does that achieve?

In this presentation, I will explain the model of communication that I developed, including the facets of communication, why it is vital, and how many of the burdens of thalassemia can be overcome through communication, with an emphasis on some adult issues: disclosure, relationships, education/employment, secondary disease, and insurance.

To achieve successful communication, barriers and considerations need to be recognized.

Barriers to communication:

- Thalassemia affects many various ethnicities–language barriers.
- There can be a lack of understanding of medical information.
- Thalassemia is complicated and difficult to explain.
- Fear of rejection; cultural and social stigmas attached to having a chronic illness, especially a blood disorder.
- Technology–look up from the phone!

Considerations in methods of communication:

- Age: upon diagnosis, the parent communicates for the child; throughout life, the patient becomes more autonomous.
- Culture: body language and eye contact. Out of respect for providers, patients may not ask questions.

Model for communication includes:

- Communication with oneself.
  Self-worth/self-esteem.
  - "I" messages: I am worthy, I am lovable, etc.
  - I am a person with thalassemia, not a thalassemic.
  - There is no NORMAL. All people on the planet have differences in their lives and health. Where diversity lives, normal does not exist.
- Communication with family.
  - Tell family members to get tested for trait.
  - Siblings–differences in their health and feelings around the disease.
  - For the health and well-being of all.
- Communication with peers in the thalassemia community.
  - Support each other.
  - Learn from each other.
  - Social media can facilitate discussion, support, and information sharing.
  - Help/advise/listen.
  - Don't get caught up in politics.
- Communication with friends.
  - Socialization.
  - Disclosure–to tell or not to tell.
  - Intimate relationships–at what point in a relationship do you disclose?
- Communication with the community.
  - School.
    - Absence.
    - Participation.
    - Educate peers and teachers.
  - Work.
    - Absence.
    - Work ethic–the need to prove yourself.
- Communication with and among providers.
  - Patient–provider.
    - Standards of care.
    - International standards.
    - Modification by country. The standard is specific to each country–care depends on education, infrastructure, availability of medical supplies and medication.
    - Collaboration; develop a partnership.
    - New treatments.

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    - Be informed.
    - Ask questions.
  - Provider–provider.
    - Standards of care–agreement.
    - Collaboration.
    - Information on latest research.
    - Transition (specific to location).
- Global communication.
  - Organizations.
    - Thalassemia International Federation (TIF): www.thalassaemia.org.cy.
    - Cooley's Anemia Foundation (CAF): www.thalassemia.org.
    - Thalassemia Support Foundation (TSF): www. helpthals.org.
    - National Institutes of Health (NIH): www. nih.gov/.
    - Food and Drug Administration (FDA): www. fda.gov/.
    - European Medicines Agency (EMA): tinyurl.com/y7kbzn6q.
  - Clinical trials.
    - www.thalassemia.org/learn-about-thalassemia/clinical-trials/.
    - www.clinicaltrials.gov/, then type in "thalassemia."
  - Governments.
    - Laws affecting thalassemia community.
    - Insurance.
  - Social media.
    - Facebook, Twitter, Instagram.
    - Laurice M. Levine–thalassemia updates on Facebook.
- Advocacy.
  - Provide community outreach—give talks on thalassemia; patient perspective. Attend health fairs, festivals.
  - Awareness of thalassemia is vital. The more people know about thalassemia, the more likely it is that services will be provided to the community.
  - Knowledge is power. If people learn about thalassemia, they will care about thalassemia.
  - Change policy that affects people with rare diseases.
  - Improved care. Work toward a cure.

Conclusions

Communication is the key to achieving a high quality of life. It is the foundation for care and can help toward a cure. Providers will learn the benefits of communication; they will have a clearer picture of what patients face. They can compassionately help patients achieve a higher quality of life by overcoming these challenges through using their voices.

Eradicate the word NORMAL. There are some challenges that are inherent to thalassemia regardless of what country the patient lives in: blood safety; access to care (even in the United States, many patients live far from centers of excellence); expertise; cost of care; social stigma and barriers that patients are working so hard to overcome. A primary way to overcome these challenges is to use our voices.

> Strength does not come from physical capacity.
> It comes from an indomitable will.
>
> Mahatma Gandhi

> You must be the change you want to see in the world.
>
> Mahatma Gandhi

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Hepatitis C virus treatment advances for thalassaemia patients

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Chronic infection with hepatitis C virus (HCV) is a major problem for thalassaemia patients, as blood transfusions before 1990 were associated with a high risk of HCV infection. Given the high prevalence of co-morbidities, thalassaemia patients are at an increased risk for dying from end-stage liver disease or hepatocellular carcinoma. HCV treatment in thalassaemia patients was challenging in the interferon-alfa (IFN) era not only due to its unfavourable safety and tolerability profile but due to necessary combined use of ribavirin (RBV) and the subsequent haemolysis and increased need for blood transfusions. The introduction of the current direct acting antivirals (DAAs), which can be used in IFN-free and RBV-free regimens, has dramatically improved the management of all HCV patients including those with thalassaemia. Currently, depending on HCV genotype and availability in each country, the main available DAAs combinations are the co-formulation of sofosbuvir with ledipasvir (nucleotide analogue NS5B polymerase inhibitor/NS5A inhibitor, one tablet of 400/90 mg once daily), the co-formulation of paritaprevir boosted by ritonavir with ombitasvir (NS3/4 protease inhibitor/ritonavir/NS5A inhibitor, two tablets of 75/50/12.5 mg once daily) perhaps with addition of dasabuvir (non-nucleos(t)ide analogue NS5B polymerase inhibitor, one tablet of 250 mg twice daily), the co-formulation of grazoprevir with elbasvir (NS3/4 protease inhibitor/NS5A inhibitor, one tablet of 100/50 mg once daily) and the co-formulation of sofosbuvir with velpatasvir (nucleotide analogue NS5B polymerase inhibitor/NS5A inhibitor, one tablet of 400/100 mg once daily). In 2017, the co-formulation of glecaprevir with pibrentasvir (NS3/4 protease inhibitor/NS5A inhibitor, three tablets of 100/40 mg once daily) and the co-formulation of sofosbuvir with velpatasvir and voxilaprevir (nucleotide analogue NS5B polymerase inhibitor/NS5A inhibitor/ NS3/4 protease inhibitor, one tablet of 400/100/100 mg once daily) were also approved and started to be used in some countries.

According to all international current guidelines, thalassaemia patients do not represent a special group for the current HCV treatment and can be treated with the same indications and regimens used for patients without haemoglobinopathies. However, in countries which still prioritize the use of DAAs according to the severity of liver disease, thalassaemia patients are often excluded from such prioritization and have access to DAAs therapy regardless of their fibrosis severity. Moreover, all guidelines recommend that thalassaemia patients should be preferentially treated not only with IFN-free but RBV-free DAAs regimens too.

In a proper clinical trial, only a 12-week regimen of grazoprevir/elbasvir has been evaluated and proven to be highly efficacious and well tolerated among patients with inherited blood disorders and HCV genotype 1 or 4 infection. In addition, different DAAs regimens have been reported to be safe and effective for the treatment of HCV thalassaemia patiens in clinical practice. Given the availability of the current effective and safe DAAs and the frequent follow-up of thalassaemia patients in a few specific units, such patients could be a targeted population for “HCV micro-elimination” on the road towards the global HCV elimination in each country.

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PIGI ZOIS: Pioneering with credibility

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Abstract

Annual transfusion requirements in Greece exceed 600000 blood units and nearly 20% of them are used for the transfusion of 3.000 patients with Thalassemia. Thalassemia patients need to be transfused properly at the right time and with safe, fresh blood. PIGI ZOIS is a nonprofit organization that tries to improve the lives of patients through providing proper voluntary blood units to patients and enhancing the Voluntary Blood Donation policy, in Thessaloniki area, which has 350 patients. The mission of PIGI ZOIS is to organize and manage almost 7.000 volunteers to donate their blood for the thalassemic patients. This is achieved by using a phone call reminder, so that the blood volunteer will donate his/her blood to a compatible young patient. All matches are done by a specialized computer program. PIGI ZOIS has donated 90.000 blood units over a period of twenty years. PIGI ZOIS also aims to raise awareness of Thalassemia through an educational program with children in primary schools, with the ultimate goal of encouraging the children to become donors when they reach adulthood. PIGI ZOIS also runs informative campaigns to the public about disease prevention and the general promotion of voluntary blood donation.

Introduction

The world is making slow progress towards the goal of 100% unpaid, voluntary blood donation, falling short of ensuring the safety and the sustainability of blood supplies. Transfusion requirements in Greece exceed 600000 blood units per year. Nearly 20% of them are used for the transfusion of 3000 patients with Thalassemia. The high prevalence of the Thalassemia gene in the Greek population along with the economic burden associated with the care of the disease, make Thalassemia a significant public health concern. Voluntary blood donation accounts for about 50% of the blood collected annually. Thalassemia patients need transfusions to be undertaken in a timely and proper fashion using safe, fresh blood.

The aim of this presentation is to show how an association of voluntary blood donors managed to successfully face this challenge.

Presentation

A Board of coordination of Transfusion Policy was established 30 years ago in Thessaloniki area, in order to give the 350 thalassaemia patients the best available transfusion therapy. Ten years later a NGO (Non-governmental organization) PIGI ZOIS ("The Spring of Life" in Greek) was founded to continue and strengthen this policy (Figure 1). PIGI ZOIS is a nonprofit organization that tries to improve the lives of patients through providing proper voluntary blood units to patients and enhancing Voluntary Blood Donation policy. Every patient has at least 10 or more voluntary blood donors fully matched for compatible blood (and not only for ABO grouping) that are called by phone (or by sms) to donate every time the patient is scheduled for a transfusion. All donors are registered electronically with their personal information, their blood group and the time of their last donation. All patients' blood groups are also registered as well as their expected transfusion day and the matches are done by the computer, with the help of a specialized software application. The mission of PIGI ZOIS is to organize and manage almost 7,000 volunteers to donate their blood for the patients with Thalassemia. This happens after a phone call reminder, so that the blood volunteer will give his/her blood to a fully compatible young patient. The donor is asked to do so in a

Figure 1. Logo of PIGI ZOIS.

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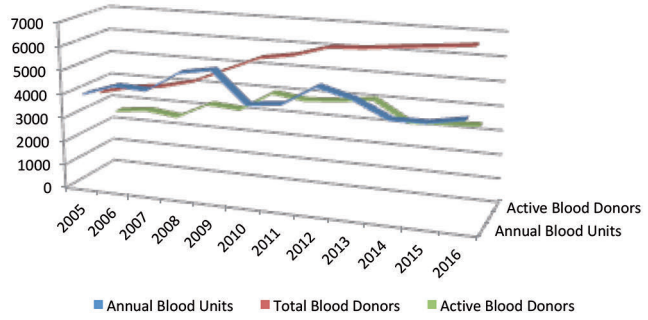

Figure 2. Total registered blood donors, active blood donors (June 2017) and Annual Blood units donated for thalassemia patients during the last twelve years (2005-2016).

period of a week prior to the transfusion of the patient. Nowadays, after 20 years of hard work, PIGI ZOIS has records of 6,929 voluntary blood donors (3,349 still active) that is constantly renewed, who donate regularly and covers about one third of annual blood requirements in the Thessaloniki area. Median annual blood donations from PIGI ZOIS reach 4,502 units (range 3973-5425). Finally, everybody gains: the volunteer gives blood 2 or 3 times per year and the patient doesn't worry about their next scheduled transfusion. All of this was made possible with the impeccable cooperation of the Local Thalassemia Association of the patients and the city's Blood Banks. Every year phone calls to donors reach approximately 10,000. Registered blood donors numbered 2,500 at the beginning of the century, 5,723 on 2010 and 6,820 on 2016 (Figure 2). Every four years all donors reaching more than forty donations are "rewarded" with a commemorative gift in a special organized public event.

Another objective of PIGI ZOIS is to inform and encourage the public about making Blood donations, as well as recruiting new blood donors to replace those that cannot donate anymore for health reasons. Of particular interest is the campaign to inform and excite children in primary schools through a "learn and play" activity based on a cartoon-program (originally made in France, 15 years ago) displaying everything about blood and its elements. This is a school-based information program on blood and donation, built around the cartoon "Journey to the Heart of Life". The purpose of the "Globulyss" (Greek word: "Hemospheria") program designed by ADOSEN and the association "Au coeur de la vie", in partnership with the French Blood Establishment, is to present in simple words the blood components and the donation procedure to children through playful and interactive media. PIGI ZOIS has translated this program (CDs and books- one for the teacher and one for the pupil) and adapted it with Greek data. We now have the permission of the Ministry of Education and we have succeeded in incorporating the project into our schools for six consecutive years with astonishing results from our youngsters. The project is scheduled to inspire altruistic behavior in the young population, thereby encouraging them to become blood donors when they reach adulthood. At the end of the academic year every participating school presents small plays, songs, paintings or games inspired by the program, at a festival that promotes volunteering.

PIGI ZOIS participates every year in the celebration of World Thalassemia Day by an informative campaign in the streets of Thessaloniki, in order to make people aware of the disease and to recruit new blood donors. This is achieved by handing out brochures about the disease and emphasizing the benefits of the National Prevention Programme, originally initiated in 1974 and already successful in reducing affected births. However, in recent years new cases have been recorded from the refugee population that has reached Greece from areas of high Thalassemia prevalence.

PIGI ZOIS is usually funded by donations and by the annual members' fees and is run primarily by volunteers. Other sources of finance include two annual bazaars (every Christmas and Easter) and cultural events, like concerts. The organization has received local and national awards for its commitment to the purpose of augmenting voluntary blood donation in Greece.

Conclusions

PIGI ZOIS' pioneering action, has become a reality thanks to the support of enthusiastic fellow Greek volunteers and shows the way to achieve safe and sustainable blood supplies without neglecting the credibility of transfusions for Thalassaemia patients.

TIF conference presentation in detail

Barrister Abid Waheed Shaikh

Pakistan

Abstract

The factors determining the health behaviours may be seen in various contexts: physical, socio-economic, cultural and political. So the utilization of a health care system, public or private, formal or non-formal, may depend on socio-demographic factors, social structures, level of education, cultural beliefs and practices, gender discrimination, status of women, economic and political systems environmental conditions, and the disease pattern and health care system itself. Policy makers need to understand the drivers of health seeking behaviour of the population in an increasingly pluralistic health care system. Also a more concerted effort is required for designing behavioural health promotion campaigns through inter-sectoral collaboration focusing more on disadvantaged segments of the population.

Thalassaemia is the most prevalent genetic blood disorder in Pakistan. It is estimated that there are 8-10 million Thalassaemia Minor cases in the country with a prevalence of 5-6%. It is also estimated that about 100,000 patients suffering from Thalassaemia Major exist in Pakistan and every year this number is increasing by about 6,000. Pakistan is witnessing this large increase in thalassaemic patients due to a lack of proper coordinated, nationwide efforts to contain the inherited form of anaemia, and general public awareness.

Different research studies and diagnosis services are carried out in Pakistan on Thalassaemia prevalence. One such service for prenatal diagnosis of β-thalassaemia was introduced in Pakistan in May 1994. Two renowned Islamic scholars, consulted before the service was introduced, ruled that a pregnancy can be terminated if the fetus is affected by a serious genetic disorder, and if termination is before 120 days (17 weeks) of gestation. During the first 3½ years of the service 300 couples requested the test. Almost all the couples had been informed by their treating doctors. Most diagnoses were made between 10 and 16 weeks of gestation, and only 15 (5%) were reached after the 16th week. DNA analysis was by the amplification refractory mutation system (ARMS). A multiplex ARMS was developed in which three primer combinations identified the mutations in 91.5% of the couples. In 13 couples (4.3%) linkage analysis was required for the fetal diagnosis. In 47/53 (88.7%) women carrying an affected fetus the pregnancy was terminated. In six cases it was declined principally on religious grounds. Postnatal confirmation of the prenatal diagnosis was possible in 117 unaffected children. One year after the start of the service, interviews with 141 couples with an affected child showed that 72% knew of the availability of prenatal diagnosis. Thirty-two of the informed couples had had a pregnancy, but only 18 (56%) used prenatal diagnosis. The main reasons for non-utilization of prenatal diagnosis were the cost of the test and fear of undergoing the test, though some gave no clear explanation. This study demonstrates that prenatal diagnosis is feasible and acceptable in a Muslim country such as Pakistan (Shoaib, Salim 2000).

Another study on Pakistan characterized 1216 beta-thalassaemia alleles from the five major ethnic groups of the country. The complete spectrum comprised 19 different mutations. There are important ethnic and regional differences in the prevalence of mutations. The five most common mutations, IVSI-5 (G-C) (37.3%), Fr 8-9 (+G) (25.9%), del 619 (7.0%), Fr 41-42 (-TTCT) (6.7%) and IVSI-1 (G-T) (5.4%), constitute 82.3% of the total. Fr 8-9 (+G) is the most common mutation in Northern Pakistan (41.3%), whereas IVSI-5 (G-C) is the most frequent mutation in Southern Pakistan (52.2%). Six subjects with transfusion-dependent thalassaemia major showed only a single mutant allele. One subject with transfusion-dependent thalassaemia major showed a novel 17 bp deletion involving Cd126-131. Our findings provide a comprehensive basis for carrying out prenatal diagnosis of thalassaemia in a geographical area where it is found in high frequency (Ahmad, Saleem 1996).

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Brief country profile of pakistan

The Indus Valley civilization, one of the oldest in the world and dating back at least 5,000 years, spread over much of what is presently Pakistan. During the second millennium B.C, remnants of this culture fused with the migrating Indo-Aryan peoples. The area underwent successive invasions in subsequent centuries from the Persians, Greeks, Scythians, Arabs (who brought Islam), Afghans, and Turks. The Mughal Empire flourished in the 16th and 17th centuries; the British came to dominate the region in the 18th century.

The separation in 1947 of British India into the Muslim State of Pakistan and largely Hindu India.

South Asia

Total Area: 796,095 sq km
Land: 770,875 sq km
Water: 25,220 sq km
Population: 208 million (2017)
Country comparison to the world: 36

Land boundaries

Bordering the Arabian Sea, between India on the East and Iran and Afghanistan on the West and China in the North.

Total bordering Area

6,774 km, with Afghanistan 2,430 km, with China 523 km, with India 2,912 km and with Iran 909 km, Coast line 1,046 km.

It also controls Khyber Pass and Bolan Pass, traditional invasion routes between Central Asia and the Indian Subcontinent.

Safety and efficacy of drugs: What do I need to know?

Mahmoud Hadipour Dehshal

Charity Foundation for Special Diseases (CFSD), Tehran, Iran

Access to the essential medicines is an important challenge in the developing countries. To have access to the quality and affordable medicines, the pharmaceutical decision makers try different strategies. The production of generic and copy medicines is one of the strategies that if adopted based on the recognized standards and norms can be effective in raising the health status in the developing countries. According to US Food and drug Administration, "a generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. These similarities help to demonstrate bioequivalence, which means that a generic medicine works in the same way and provides the same clinical benefit as its brand-name version". To make it more understandable, you can define a generic medicine as an equal substitute for its brand-name if it has been produced based on standard norms. However, shakable regulation impairs the quality of generic and copy medicines and harms the health of consumers. NGOs including advocacy groups and scientific groups play effective and undeniable role to ensure quality of the health services which patients receive. Therefore, building a network between activists and scientists is the first step towards better quality. Since we are living in a global market and pharmaceutical active ingredients of pharmaceutical finished products can be found in different regions in the market, the second step of the battle against substandard is to make an international network between advocacy groups. The international network assists to prevent menaces of substandard medicines faster and with reliance on a scientific approach. Furthermore, in the lecture, we aim to reflect over the role of different beneficiaries including international organizations, governments, and pharmaceutical companies in ensuring the feasible and sustainable access of citizens to the essential medicines.

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TIF 2.0: The Thal e-Course and TIF expert patients' programme for disease-related education and self-management skills in thalassaemia

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Thalassaemia International Federation

Abstract

In response to the fundamental shift that has been taking place in the way chronic diseases are perceived and managed and the increasingly established role of patients as equal partners in the management of their condition, the Thalassaemia International Federation (TIF) has undertaken the design and development of a comprehensive online Expert Patients' Programme (EPP) for patients with thalassaemia. Focusing particularly on β-thalassaemia, the most severe form of thalassaemia, the goal of the programme is to develop patients' disease-related knowledge and self-care skills and enable them to co-manage their disease in a meaningful partnership with their treating physicians. An important goal of this e-course is to empower patients to advocate for the improvement of national treatment services in every affected country.

The aim of this article is threefold:

(1) Relate TIF's EPP with the goals and outcomes of other EPPs, as they are made available in the literature.
(2) Describe the rationale and distinguishing features of TIF's EPP on the basis of learning theories of knowledge acquisition and attrition, and best practices from the scientific disciplines of Human Computer Interaction (HCI) and Technology-Assisted Learning (TEL).
(3) Relay the objectives of TIF's EPP and the intended international impact in relation to TIF's mission.

Introduction

"*...little has been done to prepare patients for long-term management of their diseases [...] to accommodate their symptoms and functional limitations and deal with the emotional consequences. For their care to be effective, they must become adept at interpreting and reporting symptoms, judging the trends and tempo of their illness and participating with health professionals in management decisions."* (Lorig *et al.* 1999, p. 5).

Self-management is understood as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent to living with a chronic condition" and should necessarily include the "ability to monitor one's condition and to effect the cognitive, behavioural and emotional responses necessary to maintain a satisfactory quality of life" (Barlow *et al.*, 2002). Expert Patients' Programmes (EPPs) have been conceived as a tool for the management of chronic diseases, developing patients' self-care skills, self-efficacy and confidence and support them to achieve a better quality of life (Donaldson, 2003; Griffiths *et al.*, 2007).

Professor Kate Lorig and her colleagues at Stanford University, California were the first to tap on the value of such programmes, developing and evaluating programmes for people with arthritis. The EPP tradition was soon adopted by several countries of the world *e.g.*, in the United Kingdom, and countries in Europe (especially Scandinavia), Australasia, and North America for the needs of patients with various chronic diseases such as diabetes and in various formats *i.e.*, lay-led by trained leaders and not health professionals such as nurses (Griffiths et at., 2005). With this approach, earlier EPPs in England aspired to reduce costs for national healthcare systems by reducing patients' hospital visits based on the rationale that increasing self-efficacy (confidence) is a prerequisite for behaviour change, which through improved self-management, may influence health and healthcare use (Griffiths *et al.*, 2007).

The advent of Web 2.0 technology ushers in a new period for the health industry and EPPs, enhancing the possibilities and opportunities beyond time and physical space, fostering great potential for social support and thus new methods for enhancing self-management skills, self-esteem, and self-efficacy. Murray (2012) locates Web-based interventions in three main clinical areas: (1) self-management of long-term conditions (*e.g.*, diabetes, heart disease, arthritis, and asthma), (2) health promotion (*e.g.*, smoking cessation, alcohol reduction, sexual health, diet, and exercise), and (3) mental health (*e.g.*, depression and anxiety). Practically, Medicine 2.0 has been applied in asynchronous and synchronous communication technologies, known as Virtual Healthcare Teams and Disease-Specific Patient Communities, which have achieved high levels of participation.

Unlike other types of technologies that usually cause stress to "digital immigrants" (Prensky, 2001), and require training and time before they are satisfactorily integrated into everyday practice, Web 2.0 are already part of people's everyday life and attract people of all ages. Web 2.0 tools have been used for: (1) social networking, (2) participation, (3) apomediation (guiding patients to relevant and accurate information, without troubling the specialist), (4) openness, and (5) collaboration, within and between healthcare consumers, caregivers, patients, health professionals, and biomedical researchers (Eysenbach, 2008; Boudry, 2015; Brulet, Llorca, & Letrilliart, 2015).

The Thal e-Course is the first online component of TIF's EPP, exclusively created to fit the needs of thalassaemia patients, combining opportunities for both the acquisition of disease-related knowledge (*e.g.* thalassaemia history, facts, past and current advances in treatment and attempts to finding the final cure to prepare patients for long-term management of their diseases) and

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patient collaboration. This latter taps on the potential of social (community) support, a demonstrated valuable resource in supporting routine healthcare, encouraging patient self-efficacy in managing the disease and advocating for improvement of services.

Thalassaemia patients as a sub-group of chronic patients with particular needs for knowledge and self-management skills

Thalassaemia is an inherited condition in which the genes that are responsible for producing haemoglobin are damaged or absent. Haemoglobin is the protein inside the red blood cells that transports oxygen to the body organs and tissues. Damaged or insufficient haemoglobin causes severe anaemia (=lack of oxygen in the body) and inability to sustain human life. Thalassaemia treatment requires regular blood transfusions and iron chelation therapy, without which the patients are at increased risk of premature death preceded by poor quality of life. Decades of scientific research and clinical advances have transformed thalassaemia from a fatal disease of childhood to a chronic, well-managed disease. Patients' knowledge and self-management skills play a central role to such positive outcome. Evidence shows that well treated thalassaemia patients can lead a long and productive life, integrate and contribute to society.

Nevertheless, patient adherence to treatment is reported as one of the biggest challenges and risks for thalassaemia patients' survival and quality of life. The lifesaving therapeutic regime for thalassaemia patients imposes a challenging daily routine and imposes changes to patients' lives, especially during adolescence, changes that are not always easy to accept and/or comply with. Reports say that individuals may not comply with prescribed treatment regimens due to lack of full understanding of their importance and benefits over the adverse effects associated with non-adherence. Other factors that could reduce adherence could be fear caused by incomplete information on drug side effects, patient dislike for the medications and/or the rules around using them etc. (Odame & Kirby-Allen, 2015). Experts agree that adherence to treatment can only be achieved through a deep understanding of what the condition involves, the holistic care it requires, as well as special nationally endorsed rights for thalassaemia patients.

Thalassaemia is no longer geographically confined; immigration flows have lead a growing prevalence of the disease worldwide, calling for awareness and education on the multifarious aspects and challenges of thalassaemia treatment. As research towards the final cure for thalassaemia continues, it is widely acknowledged, - and TIF's mission - that quality of treatment services should be ensured in every affected country. Awareness and regulated treatment is especially needed in poor-resourced countries which are at severe disadvantage, lacking even basic types of treatment and facing serious challenges in blood and drug safety and availability, precisely due to the absence of regulated policies for the safe and effective treatment in line with internationally-recognised patient rights for quality treatment. Thus, educating thalassaemia patients to pass on the knowledge and to advocate for better quality services and promote advocacy is a key tool in this mission and, as such, it lies at the core of TIF's EPP.

Given the above, patients with thalassaemia constitute a particular sub-group of patients who need to be able make meaningful day to day decisions such as taking medication, making lifestyle changes, or undertaking preventive action. They need to be able to modify behaviour to minimise undesirable outcomes, adjusting their social and work lives to accommodate their symptoms and functional limitations and deal with the emotional consequences. In this light, TIF's EPP targets positive outcome on two axes: (1) individual patient benefit and (2) patient community benefit (through greater involvement in patient associations to conduct advocacy work to promote national policies, quality of treatment and ensure safe and quality treatment for patients.

Conceptual framework

Conceptually, EPPs draw on social and psychological theories (Bandura, 1977) and the hypothesis that, (patients') self-efficacy *i.e.*, ability to effectively cope with and manage with treatment, leads to the initiation of a coping behaviour - a behavioural change to promote adherence to prescribed treatment and self-manage or seek help to resolve everyday disease-related problems as they arise. The assumption underlying the development of EPPs is that patients' self-efficacy can be developed through comprehensive and scientifically sound disease-related knowledge and training, which can increase patients' self-esteem and place them in control over their disease.

Increasing self-efficacy correlates with increasing confidence/self-esteem and determines the amount of effort that the patient will place on the management of his/her disease in the short and long-term as they face obstacles and aversive experiences *e.g.*, reactions to blood transfusions and iron chelation therapies. When the patients are in control over the disease and not vice versa, the patients' quality of life improves as patients are more likely to adopt a healthy and positive lifestyle, contributing to a prolonged and healthier lifestyle (Donaldson, 2003). Furthermore, knowledge about their disease generates ability to interpret and report symptoms, and participate in management decisions.

At the same time, it has been widely accepted that patients know best how their condition affects them, the way they feel, their lifestyle and their ability to accomplish important daily and other activities, and can therefore offer unique and valuable insights about disease management to health professionals, national and international policy-makers in the areas of disease control and treatment. Patients cannot be passive recipients of treatment but active participants in the interventions that affect their everyday life and their survival (Angastiniotis & Eleftheriou, this volume). At the same time, patient input is essential in all aspects of care, service provision and research and only possible when patients are well informed on their condition and its management (ibid.) with clear, accessible, relevant, scientifically-sound and reliable health information. The goal of EPPs is to provide the necessary knowledge and tools for patients to develop confidence and skills to work in partnership with health professionals (Shaw & Baker, 2004), make informed decisions about their health, participate in their treatment, understand their symptoms and seek medical advice.

Expert Patients' Programmes: A global evaluation

Several research studies have been conducted to evaluate the impact of EPPs offered around the world against their initial objectives and delivery formats. These studies conclude that due to the heterogeneity of self-management interventions/EPPs and the lack of theoretical background is a significant factor in this outcome (Newman, Steed & Mulligan, 2004), there is not a forthright yes or no answer as to the EPPs success or failure to achieve their initial objectives (Kew, Carr & Crossingham, 2017).

Certain studies have identified modest changes in patients' self-efficacy, particularly in the case of ethnic minorities, but unclear value of these changes for the patients themselves compared with a reduction in symptoms or a gain in health related quality of life (Griffiths *et al.*, 2007). Although there is some evidence that EPPs brought improvements in health behaviours, self-efficacy and satisfaction with the health care system, there is only

limited evidence that EPPs have reached their objective to reduce visits to healthcare facilities as it set out to achieve (Lorig *et al.*, 1999; Lorig *et al.*, 2008).

TIF's Expert Patients' Programme

The underlying admission of the programme is that patients who become experts are likely to be less severely incapacitated and develop skills to cope with the physical and emotional consequences of their disease by adhering to treatment, collaborating with their treating physicians to find the best possible solutions to their individual challenges and evaluating options.

Following key principles of e-Learning 2.0, the Thal e-Course provides a Personal Learning Environment in which patients can learn about thalassaemia and acquire strong knowledge and self-care skills in terms of disease monitoring, monitoring timetables, social habits, importance of adherence to treatment, and psychological support, which lie at the basis for any success in treatment. Malamed (2016) defines PLEs as "self-directed and evolving environment of tools, services and resources organized by a person seeking a way to accomplish lifetime learning, to create, and to connect with others of similar interests".

To the best of our knowledge, the Thal e-Course (TIF's EPP) is the first educational programme that is offered exclusively to thalassaemia patients and parents using dedicated tools and approaches, such as universal design, universally relevant content, and translation, to achieve a global outreach. Such tools and approaches are framed in the premises of HCI and TEL and affordances of Web2.0 tools, and with the goal of making the course accessible to all.

Objectives

Patients who complete the Thal e-Course should be able to:

1. Acquire in-depth knowledge about their condition, prognosis, complications, treatment options, research and clinical trials, other care services, psychosocial support.
2. Improve adherence, self-esteem, self-confidence.
3. Understand important policy issues, such as patient safety and patients' rights.
4. Develop necessary skills and confidence to develop effective partnerships with doctors and other health professionals.
5. Develop necessary skills to cope and manage daily life better: problem solving, goal setting, decision-making, using resources effectively, managing pain, fatigue, anger, depression, etc.

In the long run, TIF's vision for this programme is to develop these patients into core groups of Expert Patients across countries to advocate for better quality treatment services for thalassaemia patients in all affected countries.

Methodology

The general objective of this educational initiative is to develop the knowledge of patients with thalassaemia in order to give them the skills, confidence and motivation to take meaningful decisions and play a key role as partners in healthcare decision-making that concerns their own health, but also in a wider context of national health-policy decision-making.

To do so, the design of the course applied a broad range of factors that have an impact on teaching and learning (Anderson & Krathwohl, 2001). For instance, the differentiation between "knowing that" (factual and conceptual knowledge *e.g.*, vocabulary definitions and knowledge about drug categories and classifications, organ complications) and "knowing how" (procedural knowledge *i.e.*, methods about when to use this information *e.g.*, disease monitoring, nutrition). Anderson and Krathwohl (2001) specify that combining these knowledge components provides for meaningful learning and successful problem-solving and enable learners to remember, understand, apply, analyse, evaluate and create (their own approach to the disease).

Content development

The content development for the Thal e-Course was the result of a collaborative effort, which involved veteran thalassaemia patients, medical educators, and educationalists/instructional designers. (Figure 1).

Phase 1: Content writing

A group of 6 Expert Patients was identified and invited to form the "International Core Expert Patient Group" or ICEPG. The ICEPG members were selected because of their long-term experience and knowledge of medical, psychosocial and advocacy issues and patients' needs in these areas, because of their active contribution to educational national and international activities and their excellent communication skills and commitment.

This ICEPG was given the mandate to draw from personal experience and engagement with the national and international thalassaemia patient community (patient associations) to collect topics of interest and importance for thalassaemia patients and draft a first set of patient-centred educational material. Content development process was also informed by existing TIF book publications. TIF medical staff, consultants and course directors contributed to transforming this content into written material, ensuring its credibility and scientific integrity (Figure 2).

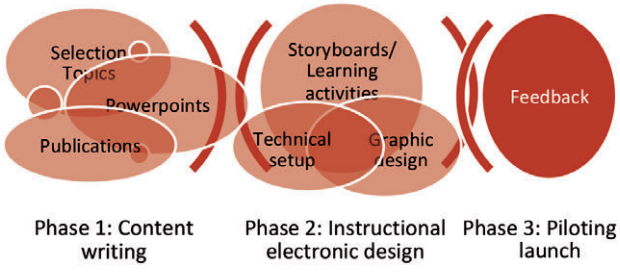

Figure 1. The development process of the Thal e-Course.

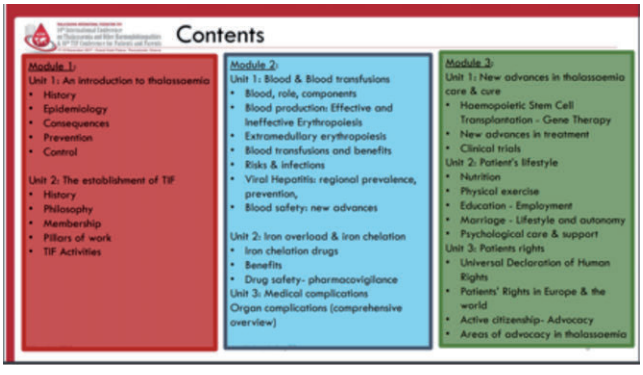

Figure 2. A summary of the contents of the Thal e-Course.

Phase 2: Instructional electronic design

Instructional designers working on this project ensured that the material were patient-friendly and comprehensible, ensured, through the strategic use of Web 2.0 technologies, and valuable insights/findings from the field of HCI and TEL, that HCI consists of the three components (1) user, (2) computer, and (3) the interaction between (1) and (2) and the ways they can best work together. The goal in HCI is to bring the power of computers and communications systems to people in ways and forms that are both accessible and useful in our working, learning, communicating, and recreational lives (Foley, 1996).

HCI, as a theoretical framework, integrates concepts and methods from computer science, design, and (ecological) psychology indicating that interfaces should be efficient and accessible to the users, and comprise opportunities for user action in order to contribute to his/her cognitive development (Figure 3).

HCI guiding principles (Norman, 1988), were combined with the Flemming and Mills' learning styles – The VARK[1] modalities (1992) and Gardner's Multiple Intelligences[2] (1996) – theories that account for best practices in pedagogy, and cater for affording opportunities for learning to patients (Table 1).

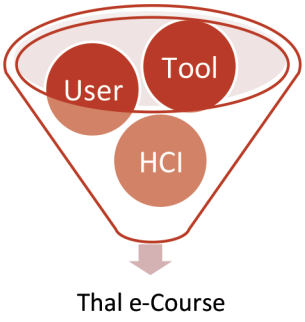

Figure 3. Instructional design methodology

[1] VARK: Visual, Auditory, Read-Write, Kinaesthetic.

[2] Moving beyond the traditional IQ-based notion of intelligence and acknowledging the existence of 8 intelligences: Visual-Spatial, Auditory, Verbal-Linguistic, Logical-mathematical, Bodily-Kinaesthetic, Musical-rhythmic-harmonic, Interpersonal, Intrapersonal, Naturalistic.

Table 1. Activity and rationale breakdown for the Thal e-Course.

HCI Component	Profile	Actions taken
User	Global thalassaemia community, (different knowledge needs) Different learning styles Multiple Intelligences Different comfort levels with technology Different language levels Varied baseline in terms of thalassaemia-related knowledge	Adjusted factual knowledge re thalassaemia according to country specifics Primary and secondary information with summaries, relaunching and quizzes Content adjusted using assets *e.g.*, videos, audios, timelines, graphics, infographics, quizzes, forum (discussion board-DB)) Translations to 5 key language of the targeted population *e.g.*, English, French, Arabic, Italian, Greek. All level appropriate through topics covered and language used
Tool (Moodle platform, course)	Web-based: allows global outreach Allows for record keeping Allows for social interaction Allows for tactile communication Easy to use Established learning system	Statistics, constant monitoring of progress Application for six principles of effective design (Norman, 1988) *i.e.*, visibility, feedback, affordance, mapping, constrains, consistency, intuitive. Engaging features *e.g.*, popups, quizzes, DB etc.)
Interaction user-tool	Different comfort levels with technology Different country specifics and needs Social support- a key aspect in thalassaemia management Tool allows for tactile communication	User-centred design: extensive attention to usability goals, user characteristics, tasks and workflow are given at each stage of the design process Course content (lay language), forum, learning activities, Quizzes: drop-down, drag and drop DB: synchronous & asynchronous interaction through a dedicated forum

Phase 3: Piloting & launch

Before final launch to the international patient community, the course was reviewed by TIF medical experts, the ICEPG (with varied technical knowledge and comfort level), and piloted by a small group of international patients in the context of a regional conference.

The target audience of this educational initiative consists of patients with thalassaemia in all *'affected'* countries, and by extension their parents/families (at a later stage). The patients can attend this course in the comfort of their home and at their own time and pace, and are given the opportunity to discuss with experts on the various topics presented in the 3 modules that comprise the platform.

Results

Participant selection for the Thal e-Course consists of the following criteria: different language levels (CEFR: A1-C2), patient different baseline knowledge (motivation letter), participants from all affected countries, all patients with thalassaemia major.

Evaluation strategies

The impact of this course will be evaluated against its initial objectives using a mixed-method approach (quantitative and qualitative). Evaluation tools comprise progress statistics, pre and post-questionnaires on experience and impact on their knowledge, self efficacy scales evaluating also self-esteem, confidence in disease-related aspects of their life, and follow-up interviews at short (immediately after the course) and long-term. Other evaluation studies will also be pursued accordingly.

Conclusions

TIF's EPP is a Web-based intervention programme, especially designed for the particular needs of thalassaemia patients and seeks, amongst others to improve the knowledge, awareness, and understanding of patients regarding their disease via the provision of scientifically sound disease and health-related material uniquely delivered via interactive Web-based components (Barak *et al.*, 2009: 4). Ensuring that patients comply with their treatment regimen, helps improve their health status and slows down the progression of disease/ complications. Knowledgeable patients can participate in patient communities and, very importantly, advocate for better healthcare services at the national and international level by offering unique insights based on experience at the national and international level.

At the same time, the changing doctor-patient relationship designates a patient who is more "involved" in their treatment (Shaw & Baker, 2004); "resourceful" (Muir-Gray, 2002) or "autonomous" patients (Coulter, 2002). Empowering patients with knowledge and skills to provide those insights, that is enable them to have a say, take action shaping drug development processes and availability in every affected country for every affected patient, and influencing healthcare decision-making are central goals of many expert patients' programmes, currently in vigour, including TIF's Thal e-Course.

The Thal e-Course is the first web-based component of TIF's especially designed to fit the needs of the global patient community suffering from thalassaemia major with regard to disease-related knowledge, adherence to treatment, current advances, and patients' rights. As such, the uptake of the Thal e-Course by the global thalassaemia patient community is worthy of close monitoring and evaluation so as to trace its potential for marking an international impact in patient education and bring about positive outcomes in patient empowerment for effective policy-making on thalassaemia prevention and management in every affected country. It is also worthwhile to note whether the Course has the potential in fostering positive patient-reported outcomes in terms of adherence to treatment and quality of life.

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Thalime: A mobile app designed just for patients and their families

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Abstract

Introducing the first mobile app designed specifically for the Thalassemia community; Thalime, your personalized private community. Thalime is a free app that connects patients and caregivers of Thalassemia to others who know what you're going through. Learn about your condition from a trusted source. Improve your well-being with health-tracking tools. Get support from others just like you. With personalized disease management tools designed to make life easier every day, Thalime is your all-in-one health resource that empowers you to be in control of your health. Build your private peer community to learn, share and receive support.

Follow programs and set goals with our personalized recommendations and virtual coaching.

Track your progress with our visual health tracker for blood transfusions and medication tracker. Additional health tracker tools allow you to monitor and share your mood, energy, pain and more.

Introduction

Thalime is a mobile app developed for those affected by Thalassemia to connect with a digital community, track their own health, and receive educational content about their disease. The app is for anyone impacted by Thalassemia, including patients, caregivers, family members, and friends. The app connects people to someone who best understands their journey with the disease; another user who is also going through the same experience (Figure 1). A health condition creates a strong connection between users, and the shared learning and emotional support from others helps patients make decisions. For over a decade, the positive impact social support on patients has led improved disease outcomes. We provide a disease-specific digital social network moderated by a community manager and maintain privacy standards to give people a safe environment to connect with others.

Engaging patient tracking tools and a news-feed of curated content educates the user about their own condition and ultimately, the patient becomes more involved in their health. Patient-centred healthcare is built on information sharing, collaboration, customization, transparency, and patient choice[2]. Curatio puts healthcare in the hands of the patient with disease specific tracking tools and customizing educational content, increasing a patient's ability to make informed decisions and take responsibility for their care. The tracking tools allow for continual patient-participation in their own health and consist of easy-to-use data entry screens for relevant symptoms, medications, and treatments. The information can then be seen in a graphical display, and users are alerted if there are abnormal trends in their data. Customization is further made possible with AI and machine learning applied to the newsfeed content and improved user-user matching over time.

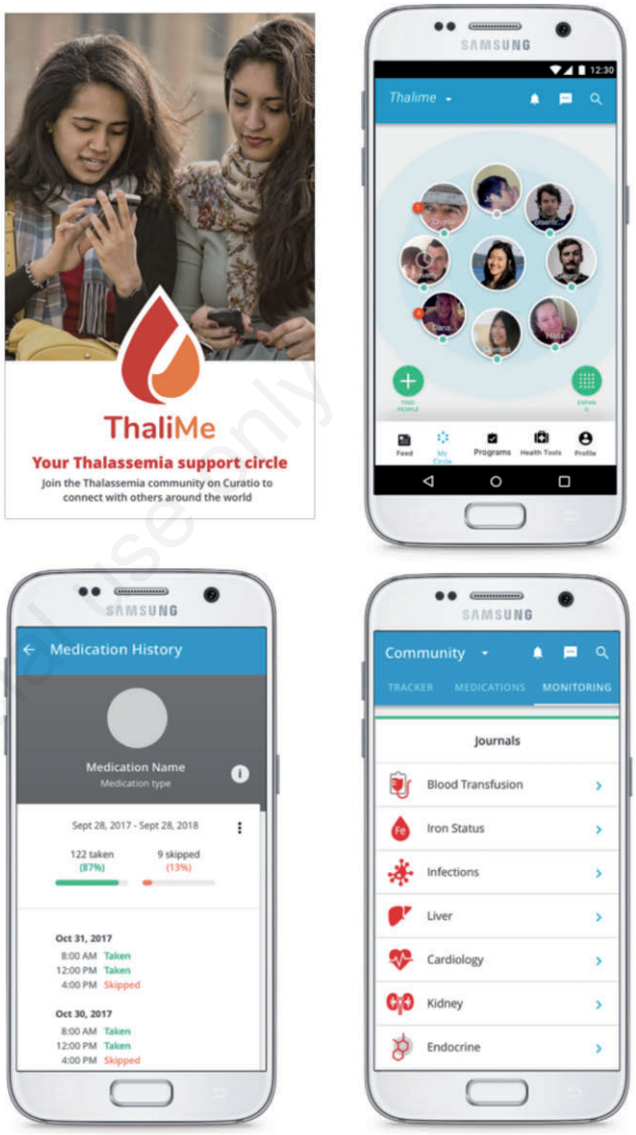

Figure 1. Private support circle, health journal, and medication tracker (clockwise from top right).

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