Genome Editing & Thalassaemia

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Thalassaemia International Federation (TIF)

**MISSION**
The development and implementation of national disease-specific programmes for thalassaemia in every country, including prevention and clinical 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.

**GOVERNANCE**
Regulated by a legally binding constitution, the Federation is presided over by a 16-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.

**CORE VALUES**
- Transparency, ethos, accountability, independence and patient-centredness.
- Health and social equity within and across countries.
- Improving knowledge and competence for the establishment of strong patients' voice.

Today represents: 204 National Thalassaemia Associations from 62 countries
What is Thalassaemia?

**THALASSAEMIA** is a hereditary (genetic) blood disorder. Together with sickle cell disease, they belong to the family of Haemoglobinopathies or Haemoglobin Disorders. It is a polyorganic disease that requires well structured, multidisciplinary approaches in the context of national programmes within the healthcare systems

‘a global disease’

- Approximately **7% of the global population** is a carrier of an abnormal haemoglobin gene
- **300,000 children are born** each year globally, due to the lack of effective prevention programmes

*Prevalence stretches beyond the indigenous population of the Mediterranean (especially Greece, Cyprus and Italy) to countries of the Middle East through to South East Asia, and increasing prevalence in Northern Europe and America due to migration population flows*  

*Source: March of Dimes, 2006*
Effective **prevention** + appropriate **treatment**

= 

↑ life expectancy  &  ↑ quality of life 

*but,*

**Inequalities** in access to quality healthcare in medium & low resource countries

=  ↓ life expectancy
What does it mean to live with thalassaemia?

Treatment

Blood Transfusion Therapy
Keeping a Hb level above 9g/dl → transfusion every 2-4 weeks

Concerns:
- Blood Safety
- Availability
- Adequacy

Monitoring iron levels and complications to vital organs
This means tests:
- Every 3 months lab
- Every 6 months lab
- Every year MRI and specialist visits

Can we afford the time and the costs?

Iron Chelation Therapy
A daily task for all days of our lives – taking subcutaneous or oral medication

Concerns:
- Iron Overload in Heart, Liver and other Organs
What does it mean to live with thalassaemia?

Complications of TDT

- Endocrine
- Liver
- Renal
- Endocrine
- Endocrine
- Cardiac
- Infections
- Bone disease and skeletal complaints

Iron overload end-organ iron toxicities are inevitable in the absence of intervention therapy.
Ongoing Clinical Trials for thalassaemia (and other Hb disorders)

- **Ruxolitinib (a JAK2 inhibitor):** reduces ineffective erythropoiesis and splenic size, with slight improvement in Hb levels. Already marketed for myelofibrosis.

- **Luspatercept ('BELIEVE' Study in Adults with TDT β-thalassaemia):** This is an erythroid maturation agent, which reduces the need for blood transfusion reducing transfusion intervals by at least 33%. Phase 3 clinical trials have confirmed efficacy and safety. Marketing authorization will be sought in 2019.

- **Hepcidin:** A liver-produced agent that regulates iron absorption which also plays a role in red cell production. Synthetic human hepcidin by LaJolla and mini-hepcidin are now in early human trials.

- **Gene therapy:** various companies have started trials. The most advanced one in human clinical trials is Bluebird Bio with LentiGlobin gene therapy and the Northstar trials, which have been granted ‘accelerated assessment’ to reduce active review time, by EMA and Orphan drug status and Breakthrough Therapy designation by FDA.

- **Gene editing:** both CRISPR and Zinc finger technology are now in early clinical trials. Companies such as CRISPR Therapeutics, Vertex Pharmaceuticals, Bioverative Therapeutics Inc., Sangamo Therapeutics and others are aiming to increase HbF in thalassaemia patients via different approaches to counterbalance the consequences of the defective gene.
<table>
<thead>
<tr>
<th>Curative methods</th>
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</thead>
<tbody>
<tr>
<td><strong>Haemopoietic stem cell transplantation (HSCT), (aka Bone Marrow Transplantation)</strong></td>
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<tr>
<td><strong>Aim</strong>: To transfer stem cells from a healthy compatible donor into the blood of a thalassaemia patient, to start producing a supply of new cells to replace those with the genetic defect</td>
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<tr>
<td>Benefits?</td>
</tr>
<tr>
<td>Concerns? Dilemmas?</td>
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<tr>
<td>Status?</td>
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<tr>
<td><strong>Gene therapy (investigational)</strong></td>
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<td><strong>Aim</strong>: Replace the defective gene or non-functional gene in patients’ DNA with a functional one.</td>
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<td><strong>Gene editing (investigational)</strong></td>
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<td><strong>Aim</strong>: Produce another condition/increase the expression of another gene that produces HbF to counteract the consequences of the defective β-globin defect.</td>
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**Haemopoietic Stem Cell Transplantation (aka Bone Marrow transplantation)**

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<th>Benefits</th>
<th>Concerns</th>
<th>Status</th>
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<tr>
<td>• Curative effect but does not change the genetic backdrop.</td>
<td>• Chemotherapy</td>
<td>The only accepted curative method to date with the highest success rate</td>
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<tr>
<td>• Easier or very confined need for the management of problems related to</td>
<td>• Fertility</td>
<td>(provided that patients have fully matched sibling donors, a healthy</td>
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<tr>
<td>thalassaemia (e.g., iron overload, chronic hepatitis, heart and endocrine</td>
<td>• Does not cover &gt;30% of the patients (those who don’t have an HLA fully</td>
<td>liver, little iron overload, and are under 16 years of age)</td>
</tr>
<tr>
<td>problems)</td>
<td>matched sibling donor</td>
<td>Still investigational</td>
</tr>
<tr>
<td>• Damaged organs may even sometimes heal.</td>
<td>• a risk of treatment-related mortality, graft failure,</td>
<td>• Cord-blood donors</td>
</tr>
<tr>
<td></td>
<td>• graft-versus-host disease (GvHD) and</td>
<td>• Fully matched related donors</td>
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<td></td>
<td>• opportunistic infections, particularly in patients who undergo non-</td>
<td>• Unrelated fully matched donors</td>
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<td>sibling matched HSCT (BMT).</td>
<td>• Haploidentical donor (50% HLA-matched)</td>
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<td></td>
<td>• Lifelong medication treatment</td>
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# Gene Therapy

## Benefits
- No need for a fully-matched donor
- No GVHD risk
- No rejection risk
- No long term immunosuppressive therapy is needed
- One time cure?
- Final cure?
- Cure at the genetic level

## Concerns
- Chemotherapy agents
- Fertility?
- Age?
- Clinical status?
- Efficiency/ Extent of curative effect depends on genotype?
- It may not be a final cure for all genotypes
- Long term side effects? (e.g., leukemia)

## Status
Advanced clinical trials by:

1. **BluebirdBio (LentiGlobin 305 viral vector)**
   - Promising results for severe/major forms of thalassaemia
   - Very promising results for less severe forms of thalassaemia
   - Improved vector (2018) to improve effectiveness in severe forms
   - Received EMA Accelerated Marketing Authorization in 2018

2. **Orchard Therapeutics (OTL-300 product)**
   - Promising results from preclinical trials + early clinical programs for TDT patients → Priority Medicines (PRIME) designation from EMA (2018)
Existing technologies for targeted Genome (Gene) Editing

<table>
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<tr>
<th>TECHNOLOGIES</th>
<th>COMPANIES &amp; PROJECTS</th>
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<tr>
<td>1. Zinc–finger Nucleotide (ZFN)</td>
<td>1. Bioverativ Therapeutics Inc./ Sangamo Therapeutics</td>
</tr>
<tr>
<td>2. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) – CRISPR-Cas 9: CRISPR-Cpf1</td>
<td>2. CRISPR Therapeutics and Vertex Pharmaceuticals/ EDITAS MEDICINE/ Intellia Therapeutics</td>
</tr>
<tr>
<td>3. BAC (Bacteria artificial Chromosomes)</td>
<td>3. Human Genome Project</td>
</tr>
<tr>
<td>4. TALEN (Transcription activator-like Effectors nuclease) – No trials yet</td>
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2 Approaches:

1. **introducing a second genetic mutation** that causes a naturally-occurring condition called Hereditary Persistence of Foetal Haemoglobin (HPFH) (CRISPR Therapeutics and Vertex Pharmaceuticals)

2. **Altering the expression of the gene that produces HbF** (CD34+ cells are genetically edited to increase HbF production (Bioverativ Therapeutics Inc./ Sangamo Therapeutics)
# Gene Editing

## Benefits
- Efficiency (how well can a treated patient survive and function with the oxygenation power provided by HbF)
- Precision
- Simplicity
- Versatility

(based on published scientific literature and announcements by biotech companies)

Real patient results are not yet available

## Concerns
- Chemotherapy (fertility, and similar concerns as in Gene Therapy)
- Off target effects (insertions and/or deletions caused by off-target effects)
- Efficiency of delivery tools
- Toxicity of delivery tools
- Delivery to non-target cells

## Status (in β-thalassaemia)

**CRISPR Therapeutics and Vertex Pharmaceuticals:**
CRISPR-Cas 9 (CTX001): 45 patients in 2 research sites in Germany (Regensburg and Tuebingen) and at 1 research site in London
CRISPR-associated systems: Cas9; Cpf1 etc.

**Bioverativ Therapeutics Inc./ Sangamo Therapeutics:**
ST-400 Phase 1/2, 6 patients between 18 and 40 years of age.
The patients’ perspective - Patient questions

1. Will Gene Editing lead to my complete cure? Am I going to live free of blood transfusions, iron chelation therapy, hospitalizations, pain etc.)

2. Will the increase of HbF make me feel better than today’s care in the Western World where my Hb level is kept between 9-10.5 g/dl throughout? (I understand that in this mindset, patients in the developing world will have more to benefit from such progress).

3. Will I inherit side effects from the curative treatment (Gene Editing) that will make me feel worse and have a poorer quality of life than before receiving the treatment?

4. On the whole, will Gene Editing be a simpler and safer process than Gene Therapy or HSCT?

5. The challenges that countries of the developing world are facing in the treatment of thalassaemia are different and perhaps patients in the developing world will benefit more from such an innovative treatment. But what are the criteria for inclusion?

6. Are age and clinical status included in the eligibility/inclusion criteria? A big percentage of patients in the developing world have poor health, consequent to suboptimal or no treatment.

7. Will there be ongoing research for further development of the technology to minimize or even ensure ZERO off-target effects?
Last but not least...

→ initiate early discussion with Healthcare system in affected countries on the: (1) cost and (2) technological demands of implementing this curative treatment.

→ Continue involving and informing the patient, the healthcare community and all the relevant stakeholders as reliably and as accurately as possible to achieve a balance between private interest and public good.

→ Respect all ethical issues related to the patient (ensure that the treatment is safe, effective, affordable and available to all that need it)

This is a miracle that we have been waiting for many many years.

IT MUST NOT BECOME A PRIVILEGE FOR SOME INSTEAD OF A RIGHT FOR ALL.
Thank you for your attention