Blood Transfusion Multi-Stakeholder Round Table
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Leopold Brussels EU Hotel, rue du Luxembourg 35, 1050 Brussels

Realities of blood transfusion
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INTRODUCTION

The Greek Mythology and Blood

The story described by Euripides 2500 years ago, emphasized in a small phrase the dual function of blood: when Goddess Athena, gave two drops of blood from Gorgous blood to Asclepius, the God of Medicine pointing out that one drop of blood cures diseases and brings life to patients and the other can bring illness and even death.

Patient advocates themselves often admit to their carers and peers: *"We would like to believe that blood is indeed a blessing for us and we are very grateful to the donors and the authorities that safeguard its safety and adequacy, although in our minds there is always the fear that it can also at times be a curse; as it can bring to us adverse conditions, some can be life threatening and we all feel almost constantly the uncertainty and we have the fear of not having adequate blood at some point in our treatment"*

The balance between bless and curse is different in different environments and different populations across countries in the world. Undoubtedly the many decades' efforts of the medical and scientific communities and the relevant decision making bodies at the European (EU Directives), other Regional and International (WHO) level have succeeded to shift the balance albeit to different levels across the world towards the 'blessing'. Particularly true in the EU countries, North America and other parts of the developed world, where residual risk of pathogens transmission and other adverse effects related to transmission have been indeed minimized with the ultimate focus to reach zero transmission (if possible).

I have the honour to represent the global community of patients with Thalassemia perhaps the largest group of consumers of blood and more specifically of the RBC component.

THALASSAEMIA AND BLOOD

Thalassaemia is a genetic, hereditary disorder of the haemoglobin molecule of the RBC, as a consequence of which normal adult heamogobin is not produced, or produced in very confined amounts that are inadequate to allow RBCs to perform their role: the provision of oxygen to tissues and cells necessary for their normal growth and functioning.

In the absence of medical interventions such as blood transfusion therapy which is the cornerstone of management of thalassaemia, patients have poor health and quality of life and very early death before reaching the first or maximum second decades of their lives.

The disorder based on a wide heterogeneous genetic background, is characterized by an equally heterogenic array of clinical outcomes that require well coordinated, comprehensive multidisciplinary and other personalized, tailored to individuals' needs clinical and other care.

Decades of work and focus mainly by the WHO has revealed that thalassaemia, along with other haemoglobin disorders, were initially very prevalent in malaria endemic countries of the world. Intense population movements and heavy migration trends particularly in the last decades, have introduced these disorders literary into the indigenous populations of almost every country of the Western world including Western, Central and Northern Europe and are today, and for some time now, not geographically confined in the Mediterranean Region as previously thought.

BLOOD TRANSFUSION IN THALASSAEMIA

Blood transfusion therapy is the first most important pillar of the clinical management regimen of thalassaemia followed by iron chelation, to address the iron load consequent to its pathophysiology but also mainly to the iron resulting from the breakdown of the transfused blood cells. Being a multiorgan disorder, multidisciplinary clinical care is essential to address effectively the consequence of the disease and its treatment on most if not all of the vital organs of the body

The work of the WHO, the Council of Europe and the European Commission, parallel to; or in collaboration with, medical and academic experts and bodies, have provided through the years ample guidance on making a transfusion safe and effective for everyone and for patients with thalassaemia who have lifelong dependence on regular blood transfusions

The recommendations provided in TIF's International Guidelines for the Management of Transfusion Dependent Thalassaemia, as prepared by a group of experts include:

- Confirm the diagnosis of thalassaemia and appropriate clinical and laboratory for transfusion (IIA).
- Use careful donor selection and screening, favoring voluntary, regular, non-remunerated blood donors (IIA).
- Before first transfusion, perform extended red cell antigen typing of patients at least for C, E, and Kell (IIA).
- At each transfusion, give ABO, Rh(D) compatible blood. Matching for C, E and Kell antigen is highly recommended (IIA).
- Before each transfusion, perform a full cross-match and screen for new antibodies, or in centres that meet regulatory requirements, perform an electronic cross-match (IA).
- Use leucoreduced packed red cells. Pre-storage filtration is strongly recommended, but blood bank pre-transfusion filtration is acceptable. Bedside filtration is only acceptable if there is no capacity for pre-storage filtration or blood bank pre-transfusion filtration (IA).
- Use washed red cells for patients who have severe allergic reactions (IIA).
- Transfuse red cells stored in CPD-A within one week of collection and red cells stored in additive solutions within two weeks of collection. (IA)
- Transfuse every 2-5 weeks, maintaining pre-transfusion haemoglobin above 9-10.5 g/ dl or higher levels (11-12 g/dl) for patients with cardiac complications (IA).
- Keep a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient (IIA).
- Keep the post-transfusion haemoglobin below 14-15 g/dl (IIA).

The above are necessary to combat the anemia, prevent or minimize bone marrow hyperactivity and organomegaly and promote normal growth and physical activity.

CHALLENGES GLOBALLY AND IN EUROPE

Despite ample knowledge and experience of how to effectively prevent and appropriately treat this disorder, many challenges exist globally and in Europe:

- Absence of truly universally covered health care systems supporting the needs of chronic patients which inevitably, results in economic catastrophy of patients and their families and in addition eventually to suboptimal or no care at all (mainly in the developing world);
- Absence to a variable extent, in many countries, including Europe, of the culture and recognition of the value and contribution of voluntary, non-remunerated blood donation policies to the safety of blood - Insufficiency of blood or collection of blood through different polices jeopardize its safety and its regular use at levels necessary to reach transfusion goals in thalasseamia (as described in International Guidelines);
- Lack of robust infrastructure in public health that would support centralized, nationally coordinated Blood Transfusion Services to support effectively patient populations like thalassaemia contribute to morbidity at various levels (mainly in the developing world).

  In the above context, services and elements, the absence of which jeopardise the health and quality of life of patients (mainly in the developing world), include:
  - Quality assured pathogen screening labs;
  - Preventative measurements for alloimmunization and development of autoantibodies;
  - Filtration of RBCs concentrate;
  - Adoption of international standards of transfusion for thalassaemia; aiming to raise and keep heamoglobin at levels sufficient to prevent the genetic consequences of the disease (as described before);
  - Effective implementation of haemovigilance programmes;
  - Policies for the appropriate storage and transport of blood;
  - Consideration of the age of blood;

Other key health priorities in the developing world still prevent to a large extend, the adoption and implementation of the Guidelines or the prevention and clinical management of heamoglobin disorders.

CHALLENGES IN EUROPE

In Europe, and although universal coverage, health care systems, robust haematology and public health services are in place, are available and accessible to patients and the magnitude of transfusion related adverse reactions and other aspects of care is anticipated

to be significantly lower than in most developing countries, there are still challenges in Europe as well and in fact more and more are emerging.

In Europe, these challenges, concerns or even better threats to the patients, their families, the society and the health care systems are consequent mainly to the Rarity of this haematological disease and include:

1. Lack of very limited knowledge and experience on the prevention and management of these disorders by mainly haematologists (to a less degree by pediatricians). This results on many occasions in almost every European country, particularly the Northern ones that are more recently receiving and hosting patients with these disorders,
    i. in the provision of suboptimal health and other care. Many patients are isolated, under transfused with all the negative consequences of these disorders' natural progression and in the
    ii. absence or lack of development of well-coordinated comprehensive multidisciplinary care and of the appropriate number (relative to the size of the country and the problem) of expert treating or reference centres.

2. The absence of national holistic prevention programmes (including community awareness, genetic counseling, screening) in almost every European country and the intense migration flows result inevitably in the increase of numbers of patients with thalassaemia and other haemoglobin disorders.

3. In the absence of national registries, the national health system cannot plan promptly to develop appropriate services and policies for these patients.

4. Existing patients, as they are aging, and patients with NTDT that are recommended, (based on current published international Guidelines), to receive transfusion, lead to significant increases in the need of blood. Considering that NTDT may constitute 15%-25% of the haemoglobin patients in every country (based on estimations deriving from registries in Greece, Cyprus and Italy), these needs will indeed increase significantly in the near future.

5. Ageing patients and transfused, previously NTDT patients, have increased risks of adverse reactions to transfusion particularly alloimmunization[1] (since residual risk of infection pathogens transmission is at minimal levels in almost every European country). Immigration and widely different ethnic backgrounds constitute additional risks of increased alloimmunization and in all cases serious challenges emerge in finding appropriately matched donor.

6. In addition, more recently, scientific evidence that begin to emerge calling for revisiting the transfusion Guidelines with an indication for much earlier onset of regular transfusion, raises deep concerns related to adequate supplies of blood.

7. Social care to take patients and their families out of isolation and provision of more constructive support for accessing already available services in the country the patient lives, such as for example supporting travelling and/or reducing to the minimum the need to travel for blood transfusion, are key issue of framing the patients' perspective (as expressed through visits, personal discussions and surveys conducted by Thalassemia International Federation (TIF).

[1] **Alloimmunization - a major complication of transfusion in multiply transfused patients**

Risk factors are complex and involve at least 3 elements: (i) RBCs antigenic differences between donor and recipient, (ii) the recipients' immune system and (iii) the immune-modulatory effects of the transfused RBCs on the recipient

Serious complications may occur, such as life threatening delayed haemolytic transfusion reactions and transfusion delays due to difficulties in finding compatible units. Most common are those against Rh, particularly C and E antigens and the Kell system, followed by Kid, Duffy, Lewis and MNS systems.

Reported rates vary according to the extent of compatibility processed RBCs antigens matching, the degree of homogeneity between the recipient and the donor, ethnic backgrounds and the frequency of transfusion. It would vary between 18% to a high as 76% in SCD patients receiving only A, B, O and D matched RBCs to 5% - 11% with addition limited antigens phenotype matching for C, E and K antigens and to 0% - 7% with extended phenotypes matched RBCs. Autoantibody formation may be triggered with a cumulative incident of 6% - 10%.

In thalassaemia major, patients alloimmunization ranges from 5.2% - 37%, although could be lower in more homogeneous populations, although migration intensification in Europe is disrupting the homogeneity of the population in many European countries.

Alloimmunization is more common on thalassaemia intermedia related to splenectomy, pregnancy and history of no prior transfusions

Risks of autoimmunization should also be considered. In a recent study the 1% identified 16.5% autoantibodies – older age and splenectomy were associated irks factors and 84% of patients with autoantibodies were also alloimmunized.

The public health services in European countries, are expressing from their perspective (based on TIF's work), their concerns that any increased needs for blood for addressing the management of these disorders, as well as the uptake of measures to further safeguard the safety (NAT testing and molecular phenotype) and efficacy of blood transfusion therapy, as well as to promote strategies for the prevention of thalassaemia for the indigenous population and additional policies and programmers to reach out to the migrant populations, entail heavy costs in the context of health care systems struggling for sustainability and resilience and in a European and global environment of severe financial constraints.

CONCLUSION

Patients/families/health care professionals and public health stakeholders are seeking NEW TOOLS, NEW ADVANCES, to decrease the needs for regular blood transfusions and where possible to have patients independent of transfusion.

What do patients say?

"We need new advances that would untie our lives and our hands from long hours of lifelong blood transfusion."

"Blood transfusion could be a bless but could be a curse for us and each time we feel the uncertainty and fear of its outcome."

"Transfusion therapy is disturbing our social and professional lives"

What do public health stakeholders say?

"We need more blood for a lot more medical disciplines today."

"We need to reduce costs related to safety and efficacy of transfusion therapy of complicated, multi-organ without jeopardising their health and quality of life."

TIF is in the process of completing a global report in collaboration with the WHO and in its commitment as an NGO in official relations.

The report is focused on mapping as accurately as possible the existing services, strengths, successes and weaknesses across countries members of TIF (in the 6 WHO regions). It aims to provide the evidence and tool for TIF to prepare suggestions and offer its expert support to countries that are in need and wish to have it. The objective being always to support build effective national programmes where countries are in need for realizing its

mission and vison of establishing equal access to quality healthcare for all (in the context of patient-centered, universally covered health care systems – *Health in the SDG Era, WHO Sustainable Development Goals, Goal 3: Good Health & Well Being*)