

GENE THERAPY in β -thalassaemia and other haemoglobin disorders

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An educational leaflet (No2)
for the patient



THALASSAEMIA
INTERNATIONAL
FEDERATION



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Gene Therapy in β -thalassaemia

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Introduction

Recent developments in gene therapy for β -thalassaemia have brought hope that multitransfused β -thalassaemia patients will, in the very near future, have a chance and a choice for a one-time final cure and a life without the need for treatment.

For some years now, gene therapy has been seen as a great promise for the cure of several serious diseases and in particular for genetic disorders.

Some of the most successful gene therapy products to date for hereditary genetic disorders, include those for primary immunodeficiencies where gene therapy has already been shown to be a life-saving, life-extending treatment leading to dramatic improvements in health and quality of life. Inherited retinal diseases, spinal muscular atrophy and haemophilia constitute other examples. This gives substantial hope for future progress in treatment of many other genetic conditions.

Despite these advances, gene therapy has not yet delivered as many clinically available treatments as expected. During recent years, however, the number of ongoing gene therapy clinical trials has increased rapidly and patients all over the world are very excited and filled, on the one hand, with optimism and hope and on the other hand with concerns on the effectiveness, safety and accessibility just to mention they key ones.

"Patients and patient organisations are amongst the keenest advocates for research and development in gene therapy. Their benefit is not in getting a scientific degree or title, earning money or even being on the news. Their benefit is in improving health and overcoming a life-threatening disease, in cure rather than care"

(EGAN, Gene Therapy and Ethics: the Patient View, A tool for public dialogue, July 2009).

This leaflet, created by the Thalassaemia International Federation (TIF) with the support and guidance of TIF's medical expert doctors, aims to strengthen the knowledge and understanding of thalassaemia patients across the world on most aspects relevant to gene therapy. It is noted however that some aspects still cannot be publicly disclosed, whilst others require post-authorisation data for an adequate time period before accurate and definitive conclusions can be made.

Through this leaflet, every possible effort is made by TIF to clarify, with the support of its scientific/medical advisors, as far as possible, the steps in the process leading to this new radical therapy and answer as many questions as possible and to the extent possible at this point in time. Already many questions have been raised by patients from across the world through TIF's global survey on patients' perspective regarding gene therapy.

Gene Therapy in β -thalassaemia

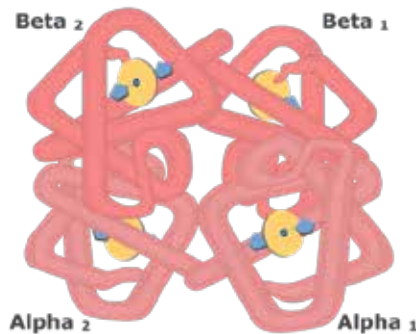
A number of gene therapy approaches for the cure of thalassaemia have developed through the decades, particularly in the last 20 years. Some have reached various stages of development and are in the context of investigational work in the form of clinical trials.

One of these however, developed by Bluebird Bio Inc, a clinical-stage biotechnology company, has recently completed successfully all the phases of clinical trials as defined by the European regulatory body - the European Medicines Agency (EMA). Its product, ZYNTEGLO™ received, on 29th March 2019, a positive opinion or a recommendation from EMA for final approval and was granted, on the 3rd of June 2019, marketing authorization by the European Commission. Patients and families can use this leaflet as a guide for further relevant discussions with their treating physicians.

Disease genetic background

Homozygous β -thalassaemia or thalassaemia major is a genetic disorder of the blood caused by the inheritance¹ of two mutated (defective, non-functional) β -globin genes³ (one from each parent). As a result of this genetic defect, the body can only produce little or no normal adult haemoglobin (HbA), the vital oxygen carrying protein of the body.

The patient with this genetic defect can only survive through extensive multidisciplinary support and care including mainly lifelong regular blood transfusions of donated red blood cells (RBCs), containing healthy Hb. Furthermore, as transfused RBCs complete their lifecycle in the blood and break down (a normal biological process of the body), they release their Hb with its iron. Thus, in addition, these patients need lifelong daily iron chelation therapy to remove this excess iron which causes, if left unaddressed, severe damage to vital organs of the body leading to high rates of morbidity and early death.



As far as radical cures are concerned, until very recently, the only approved treatment for the cure of β -thalassaemia was to give patients stem cells from the bone marrow of a healthy donor, a procedure known as bone marrow transplantation (BMT)² or haematopoietic stem cell transplantation (HSCT) (described more extensively in the relevant TIF Educational Leaflet³). The best results, however, using this approach can be achieved when the donor is a fully-matched sibling⁴. A fully-matched sibling donor is available to no more than 30% of patients in any country. Approaches that use other types of donors (alternative donors), aiming to extend the percentage of patients accessing BMT with successful outcomes, are still very limited and confined to very few BMT reference centres.

Gene therapy has been a long awaited dream of the global thalassaemia patients' community and constitutes the other approach for a radical cure, independent of the restrictions or possible side effects involved with BMT, but of course carrying its own concerns and challenges that need to be thoroughly discussed between medical experts and patients.



What is gene therapy?

Background: gene therapy has been studied for various genetic diseases since the 1980s. More than 1,800 gene therapy trials have been conducted since then. Extended gene therapy clinical trials in β -thalassaemia were approved in 2012.

It is an approach, as previously mentioned, that aims to cure genetic diseases by replacing or correcting (editing) the defective or non-functional gene in the patient's DNA. In the case of β -thalassaemia, a defect (mutation) in the β -globin gene results in the decrease or absence of haemoglobin the vital oxygen carrying protein of the body. If this gene is replaced by a functional one, then it is anticipated that haemoglobin production will be restored and consequently the patient's red blood cells will have normal function.

¹ When both parents are carriers of the thalassaemia trait, they have 25% chance in every pregnancy of having a child with thalassaemia. To avoid having an affected child, couples can get tested or screened for thalassaemia trait before they decide to have a family. The thalassaemia trait can be detected through a simple blood test.

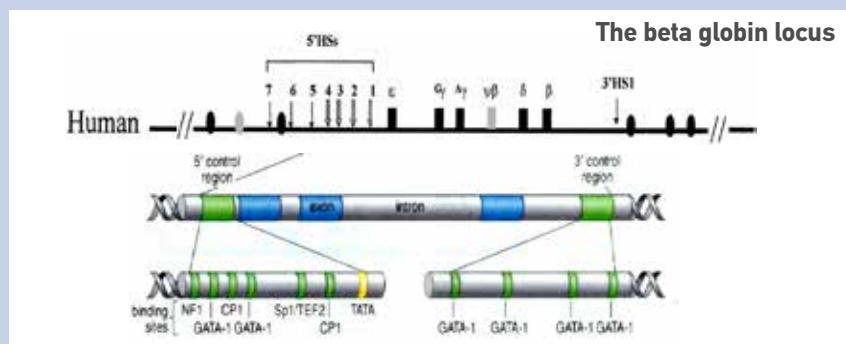
² Bone marrow transplantation is also referred to as allogeneic HSCT because it uses stem cells from an "allo" (Greek for "other") donor. Gene Therapy, on the other hand, which uses treated stem cells from the patient him/herself which are returned to the patient in an autologous transplant ("auto" is Greek for "self")

³ TIF Educational Leaflet No 1: 'Bone Marrow Transplantation in β -thalassaemia'

⁴ A fully-matched sibling donor is a brother or a sister of the patient whose cells have the same HLA characteristics as those of the patient. HLAs are proteins found on the surface of almost all cells of the body.

Below is a simplified description of the process:

1. **Blood harvest from the patient:** blood forming or stem cells derived from the marrow of the bones (their natural "home") of the patient are harvested from peripheral blood and are purified in specialized laboratories. Prior to this, the patients are given specific drugs to mobilize or stimulate and help their stem cells to move from the bone marrow into the blood in order to collect them. The greater the number of stem cells collected and processed in the specialized laboratory, the better the chances of achieving successful gene therapy. It has been demonstrated in clinical trials that the higher the "dose" of the "corrected" stem cells infused into the patient, the higher is the expression of the functional β -globin gene, which eventually leads to higher haemoglobin A (HbA) production that could render the patient transfusion independent



2. **Blood cell correction in the lab:** A healthy/functional copy of a β -globin gene, developed under specific conditions in very specialized laboratories is introduced or transferred into the harvested stem cells (as described above) using a "vehicle" or a vector, as referred to in science. Microorganisms, the smallest of which are viruses⁵, and more specifically a certain type of these, called lentiviruses, serve as the vehicle or vector for introducing the functional gene into the harvested stem cells referred to as from now "corrected" stem cells. This type of virus, before any manipulation in the laboratory, has the ability to transfer its genetic material into the DNA of human cells causing disease. When used as a vector, however, in gene

⁵ In gene therapy, viruses are used as vectors because they have a natural ability to deliver genetic material into cells. The virus is previously genetically modified in the lab to ensure that it can be introduced into the patient's bloodstream to deliver the healthy gene without harming the patient in any way e.g., causing an infectious disease. Because of its use as a vehicle to transfer the healthy gene into the patient's cells, the genetically-treated virus is called a viral vector.

therapy, this virus is genetically modified in the laboratory to become completely harmless and safe for the patient when being used to transfer the functional gene (gene of choice) to the "harvested stem cells". When this lab process is completed, the patient needs to be prepared by the doctors to "receive" these genetically modified (corrected) stem cells which contain the "right" or functional gene back into his/her blood circulation. This is a process called autologous transplantation⁶.

Autologous versus allogeneic transplantation

In the case of gene therapy the stem cells of the patient are "corrected" as described above and reintroduced into his/her circulation (autologous⁷ or self) as opposed to the allogeneic⁸ bone marrow transplantation (BMT) where the stem cells from a donor (e.g. sibling) are introduced into the patient's blood.

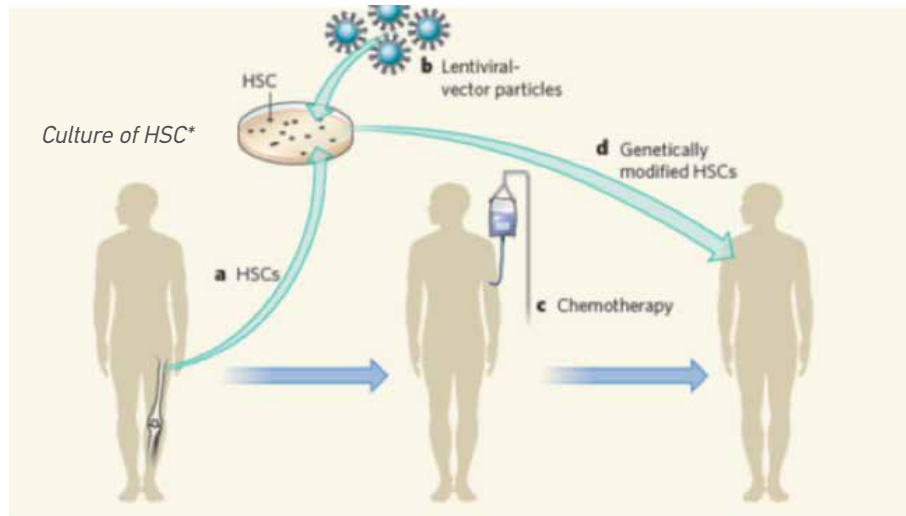


More specifically, the "harvested", "corrected" stem cells into which the functional β -globin gene has been transferred with the help of the viral vector, are returned back into the patient's blood circulation (just like a blood transfusion). These cells find their way to the patient's bone marrow, which is their natural home, and soon start producing red cells containing healthy Hb.

3. **Patient preparation/conditioning:** Prior to receiving the "harvested, corrected" stem cells back to his/her body (autologous transplantation), the patient goes through a process in the hospital called myeloablation or myeloablative conditioning regimen. This prepares (conditions) his/her bone marrow to receive the genetically modified stem cells. The conditioning regimen consists of chemotherapy drug(s) (usually used in oncology) and is needed to eradicate (destroy) the existing thalassaemic stem cells, creating the necessary bone marrow "space" for the engraftment (establishment and growth) of the corrected stem cells. The engraftment of a high percentage of genetically corrected stem cells in the patient's bone marrow is a prerequisite for the production of haemoglobin in high (therapeutic) levels, a prerequisite for the success of gene therapy.

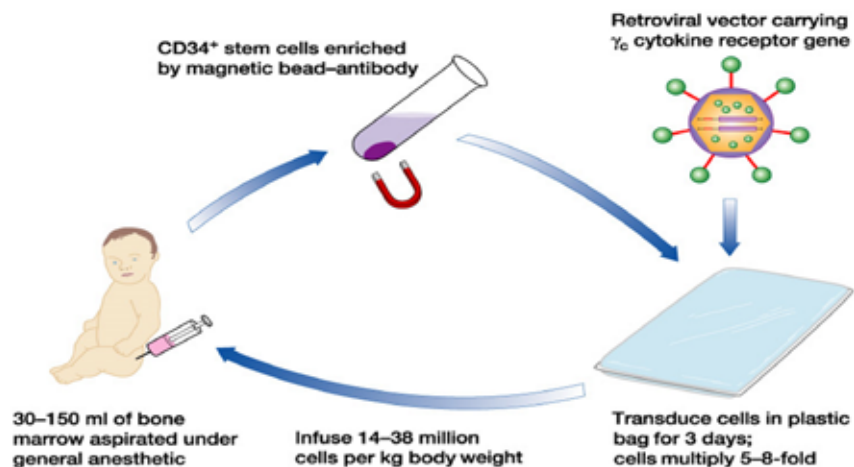
⁶ Autologous transplantation means the transplant is made up of autologous genetically modified cells
⁷ Autologous - The word is Greek in origin. The definition is exactly 'autos' means self and 'logos' means relation. Thus meaning is related to self.
⁸ Allogeneic - Definition - formed elsewhere than where it is found

Gene Therapy: Clinical Trials & Results



HSC= Haemopoietic stem cells (blood forming)

Figure: Gene therapy in thalassaemia (Persons DA, Nature 2010)



Evidence from the results of the clinical trials carried out by Bluebird Bio Inc showed that after introducing the “corrected” stem cells in multitransfused β -thalassaemia patients in the context of the gene therapy process:

- I. the majority (4 in 5) of the patients with the less severe form of the disease (those with a non- β^0/β^0 genotype or otherwise β^+ genotype) have become transfusion independent shortly after gene therapy.
- II. most patients with the more severe form of thalassaemia (i.e the patients who have the β^0/β^0 genotype, and who normally produce no haemoglobin A at all) did not actually become transfusion independent. Many of those, however, had a significant decrease in their annual transfusion requirements.

More information to date available about the recent developments:

ZYNTEGLO™ is the new product of the work of Bluebird Bio Inc and is the new therapeutic option for patients with β -thalassaemia major based on the transfer of a functional β -globin gene into the patients’ cells. Using a lentiviral vector, functional copies of a modified β -globin gene are added into a patient’s own stem cells, thereby addressing the underlying genetic cause of the disease.

Being a highly advanced cell therapy, this should only be administered in a qualified treatment centre by a physician with experience in stem cell transplantation. ZYNTEGLO™ will be used, based on the published information describing this product, for patients 12 years and older with transfusion-dependent β -thalassaemia (TDT) who do not have a β^0/β^0 genotype and for whom haematopoietic stem cell transplantation (HSCT) is appropriate but for whom HLA-matched related HSC donor is not available.

The most common non-haematological side effects observed in the relevant studies using this product were:

- stomatitis (mouth inflammation)
- febrile neutropenia (fever during neutropenia)
- epistaxis (nosebleed)
- venoocclusive liver disease
- abdominal pain

It is of note that all side effects were consistent with the myeloablative conditioning (preparative) regimen (and were not attributed to the lentiglobin gene therapy product) and that all of them resolved with or without treatment.

A positive opinion adopted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), on the 29th of March 2019, for the product ZYNTEGLO™ is an intermediate step to patients’ access to gene therapy. The positive opinion was sent to the European Commission

which granted, on the 3rd of June 2019, the marketing authorisation. Discussions will now start on identifying the centres fulfilling the scientific/medical/quality criteria for undertaking gene therapy and on the decisions about price and reimbursement at the level of each Member State. Such discussions will certainly take into account the existing situation with regards to prevalence and costs of clinical and other care of the patients in a country and the potential role/use of this product as a curative approach in the context of the national health system of that country.

Clinical trials have also started for sickle cell disease (SCD), although still at an earlier stage compared to the thalassaemia trials. The processes used are similar to those described above, using lentiviral vectors and autotransplants.

Cost

All advanced cell therapies, including gene therapy treatments, are quite costly, because of high development and production costs.

An important part of the total cost of gene therapy is the high cost of the viral vector, driven by the quantity and type of the vector with highly-skilled human resources, requirements in safety, quality efficacy and regulatory compliance to Advanced Therapy Medicinal Products (ATMPs) and GMP (Good Manufacturing Practice) demands.

Moreover, gene therapy should become more affordable in the coming years as hopefully new products are approved and increased competition between suppliers will most likely favour a decrease in the price of the gene therapy product.

While the cost of gene therapy may initially appear high, a future decrease in manufacturing costs and its curative/longlasting potential could lead to long-term savings, which in turn could facilitate payer's approval.

However, its long-term efficacy and costs still need to be assessed in order to have a more global view of long-term effects on the health care system.



Concerns

Some safety concerns have been raised in current years related to gene therapy and these include:

- i. the possible interference of the healthy gene with other genes,
- ii. the possible early or long-term complications of the chemotherapy used prior to the gene therapy procedure (e.g., severe infections or bleeding, reduced fertility, hormonal changes).

Patients views/perspective

The results of TIF's survey March 2017 - March 2019

The patients' perspective was demonstrated through analysis of the answers obtained from 1.000 participants in the last survey conducted by TIF amongst its members in 62 countries worldwide.

- Most patients aged 12-20 years old were not familiar with the gene therapy treatment and the few who were aware had limited knowledge.
- Most patients aged 21-50 years old had better, but still not adequate knowledge, on gene therapy treatment and expressed fears and uncertainty about the side effects of chemotherapy (e.g., hair loss, infertility), use of a human immunodeficiency virus (HIV)-derived viral vector, and potential for cancer risk as their younger peers.
- Both age groups focused greatly on the efficiency of the method in transforming their disease into a transfusion independent one and were eager to know :
 - i. the inclusion and exclusion criteria,
 - ii. the centers and the criteria in assigning them to perform gene therapy and
 - iii. expressed their deepest concerns as to whether governments would even consider introducing this approach in the context of their healthcare systems, the greatest majority of which worldwide, are, and have been for some years now, under economic pressures and striving to achieve universal coverage.

In summary, our findings support the importance of providing patients with detailed education on gene therapy treatment taking also into account the fact that many participants of the surveys, irrespective of age, expressed a significant level of fear that on many occasions was due to misconceptions about gene therapy treatment, its risks and side effects.

Other gene-based treatment approaches

Today, other gene-based approaches for the treatment of genetic diseases are in the pipeline. Genome editing, for example, is another gene-based approach. It allows scientists in the lab to address the cause and not just the symptoms of genetic diseases by performing a sort of genetic surgery for correcting DNA defects. Technically, genome editing tools are able to change genes by adding, replacing and/or removing sections of DNA, thus correcting the mutation responsible for causing the disease. The latest genome editing system is called CRISPR/Cas9. Published information relates this to faster, cheaper, and more accurate technology than any other system. It is also technically easy to use, which means that may be accessible to a large number of scientists and laboratories. Importantly, this technology is still being developed and it may be some years before genome editing could directly benefit rare disease patients including thalassaemia patients.

Although very promising with potentially a wide range of future clinical applications, significant scientific challenges still need to be overcome before the technique can benefit patients. Recently (2018), the first clinical trial using genome editing for gene therapy of β -thalassaemia was initiated in Germany (ClinicalTrials.gov Identifier: NCT03655678).



Thus genome based approaches in general have implications for national and international communities. Early discussions on safety, ethical issues, impact, and costs before the introduction of these techniques into the clinic, should be a priority not only for clinicians, scientists, ethicists, policy makers but also very importantly for patients.

The role of TIF thus, is extremely important in informing and educating reliably and timely, in working closely with every national patient organization around the globe towards initiating and in conducting early discussions with healthcare professionals and national health policy-makers. TIF has in addition, the special obligation of representing the global patients' perspective on gene therapy at regional, European and international fora including the World Health Organization (WHO).

Useful sites:

U.S. National Library of Medicine

Available at <https://ghr.nlm.nih.gov/primer/therapy/genetherapy>

Wikipedia

Available at https://en.wikipedia.org/wiki/Gene_therapy

Medscape

Available at <https://www.medscape.com/viewarticle/911116>

U.S. Food & Drug Administration - Cellular & Gene Therapy Products

Available at <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products>

European Medicines Agency Gene Therapy Working Party

Available at <https://www.ema.europa.eu/en/node/4853>

NIH Clinical Trials Register

Available at <https://clinicaltrials.gov/>

EU Clinical Trials Register

Available at <https://www.clinicaltrialsregister.eu/>

Zynteglo®

Available at <https://www.zynteglo.eu/>

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Your Opinion Matters to Us!!

Educational leaflets

Other educational leaflets available:

Educational Leaflet 1:

Bone Marrow Transplantation in β -thalassaemia

Educational Leaflet 2:

Gene Therapy in β -thalassaemia and other haemoglobin disorders

Educational Leaflet 3:

Clinical trials in β -thalassaemia

Educational Leaflet 4:

Iron chelation and monitoring for iron load in β -thalassaemia

Educational Leaflet 5:

Liver Disease in β -thalassaemia

Educational Leaflet 6:

MRI testing in β -thalassaemia

Educational Leaflet 7:

Effective Organ Monitoring in β -thalassaemia

Educational Leaflet 8:

Blood safety in thalassaemia and other haemoglobin disorders

Educational Leaflet 9:

Prevention of Thalassaemia and other haemoglobin disorders

Educational Leaflet 10:

New drugs and their impact on the pathophysiology and management of thalassaemia



TIF's Educational Programme (in brief)

The Thalassaemia International Federation (TIF) has developed an internationally-recognised educational programme, with the objective of providing lifelong education opportunities for healthcare professionals, patients and their families, and raise awareness amongst policy makers and the community at large. These include:

- 1 Conferences and Workshops (national, regional, international)
- 2 Fellowships and Preceptorships
 - i. Renzo Galanello Fellowship Programme
 - ii. TIF Preceptorships
- 3 Electronic and Mobile Learning
 - i. TIF e-Academy
 - Thal e-course for patients/parents
 - e-courses for health care professionals
 - ii. ThaliMe app
 - iii. TIF Digital Library

Help us get the patients' perspective on gene therapy:
Complete TIF's Survey at <http://bit.ly/2XBS2mo>

HOW TO PARTICIPATE: <https://thalassaemia.org.cy/education/>



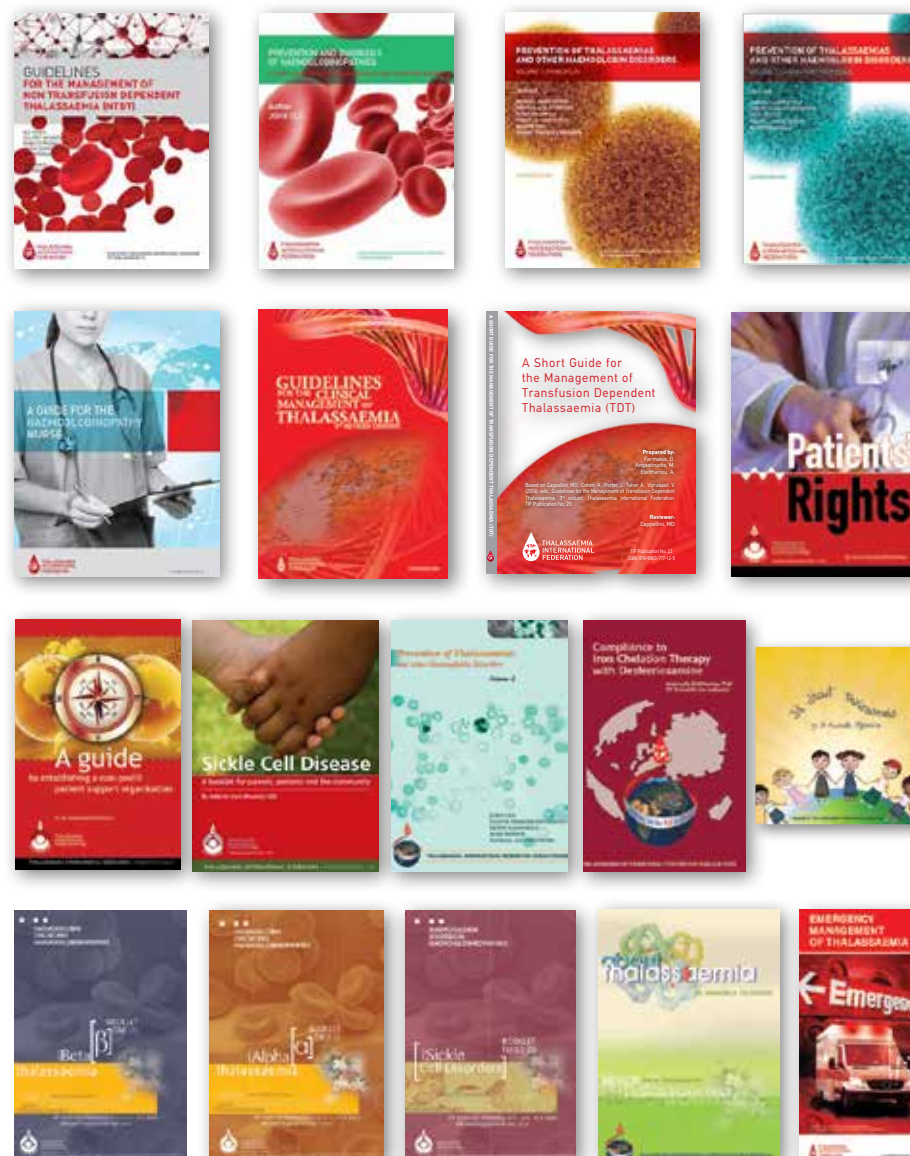
THALASSAEMIA INTERNATIONAL FEDERATION

Thal e-Course for patients

Become an expert patient!

Expert patients can delve deep into the whats and whys of their condition and make meaningful decisions about their health. Very importantly, expert patients can play a key role in the improvement of health, social, economic policies related to their condition and quality of life.

TIF's Publications



HOW TO ORDER <https://thalassaemia.org.cy/publications/tif-publications/>

A few words about Thalassaemia International Federation (TIF):

TIF Thalassaemia International Federation is an NGO founded in 1986 by a small number of patients and families representing National Thalassaemia Associations in Cyprus, Greece, UK, USA and Italy, countries in which these diseases have been recognised as an important matter for public health and where the first programmes for prevention and management were implemented.

MISSION To improve the survival and quality of life of patients with thalassaemia through the promotion and support of: education, advocacy and capacity building of patients' and their families' awareness and education programmes for the community collaboration with national, regional and international health authorities aiming to (a) prioritise thalassaemia on national, regional and International health agendas; (b) develop and implement national disease specific programmes for its effective control, prevention and holistic care, and research programmes and studies focused on the final, total cure (c) establish equal access of every patient with thalassaemia to high quality health and social care services provided through truly patient-centred healthcare systems.

VISION Establishment of equal access of every patient with thalassaemia to high quality health and social care services provided through truly patient-centred healthcare systems.

The content of this Educational Leaflet for the Patient entitled "Gene Therapy in β -thalassaemia and other Haemoglobin Disorders" represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.





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