living well with thalassaemia

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Between 300,000 - 500,000 newborns every year show a severe haemoglobin disorder and between 100,00 -150,000 are affected by thalassaemia syndromes. They have a variety of health problems in common, but they cope with their illness in different ways.

Thalassaemias can vary in type, severity, therapeutic requirements, and sensitivity to iron chelators. Because of this, patients must be informed on the most important aspects of their illness so that they can learn to manage the problems, regardless of whether these are big or small, of everyday life.

In fact, we have known for a long time that good patient 'compliance' to treatment - that is, the precision with which each patient applies his or her own therapeutic programme - is the most important way to improve their clinical condition and fine-tune their therapy.

Today, after the success in transplantation of bone marrow or placenta-derived cells, gene therapy is offering us an even bigger hope that it may be used even where transplant is not applicable or advisable.

But what can we do in the meantime? The organism needs to be kept in the best possible condition, and complications and disease progression must be avoided.

By using the available therapies according to the personal requirements of each patient, in a customised approach, excellent results may be achieved.

The physician in charge, the health service as a whole, and the patient him or herself each make their own contribution to reaching these objectives.

Continuity of treatment, therapeutic programme, and 'empowerment' - that is, the ability of the patient to influence the medical decisions taken on his or her behalf - all play an essential role.

These are based on knowledge and understanding, transparency of the current therapy state of the art, and availability of empowering tools for patient engagement that facilitate meaningful and relevant information exchange and that allow an interpretation and application of the results of medical research in a way that is critically and scientifically correct.

By pursuing the goal of providing children patients with a new syrup formulation of deferiprone, the DEEP Project (DEferiprone Evaluation in Paediatrics) makes its own contribution to achieving these results.

OBJECTIVES AND METHODOLOGY

The project, developed by the Gianni Benzi Pharmacological Research Foundation, aims to provide patients with direct access to knowledge and understanding of the numerous problems related to the treatment and cure of the thalassaemias.

This project does not intend to provide general information that is already available in other publications and from other sources (including the worldwide web), but to give detailed information in answer to those questions asked most frequently by the patients.

The information provided will try to eliminate the prejudices and common misconceptions about the illness, and are always based on scientific evidence that can be recognised and checked.

We hope that this project will help every thalassaemia patient to:

- have a more in-depth knowledge of the aspects that affect them most;

- learn how and where they can find answers to their doubts;

- be able to discuss their disease and its treatment with their doctors and healthcare professionals in an informed way.

We have chosen some of these questions concerning issues that are often met in daily clinical practice. We have talked to doctors, parents and experts in the field, and we have tried to provide accurate yet simple answers based on all the currently available knowledge.

IS IT TRUE THAT THE DIAGNOSIS OF THALASSAEMIA IS THE SAME FOR EVERYONE?

FALSE. The thalassaemia syndromes are all very different from each other both for the type of genetic defect present in the red blood cells and, above all, for the clinical manifestations and the severity of the different forms!

The thalassaemia syndromes are a group of inherited genetic diseases that are transmitted by parents to their children through their genes. These diseases are not transmitted through blood, air or water, or through physical or sexual contact. In the thalassaemia syndromes, the normal production of haemoglobin is either partly or completely suppressed because of a defect in the synthesis of one or more of the globin chains that represent the components of haemoglobin.

There are different globin chains: alpha, beta, gamma or delta.

Sometimes, the defect involves more than one chain at the same time, as in the case of the delta or beta-thalassaemias.

Beta-thalassaemias. The beta-thalassaemias are determined by alterations in the gene for the beta chain. The following cases can be observed:

- alterations of both gene copies (both maternal and paternal), with an almost complete absence of the beta chain in *thalassaemia major or Colley's disease*. This leads to cases of severe anaemia due to the early destruction of the red blood cells in the bone marrow. If this anaemia goes untreated, skeletal changes take place because the bone marrow, where the red blood cells are produced, increases in volume to try and compensate for the loss. The red blood cells that are produced are poor in haemoglobin and are quickly destroyed causing also spleen size to increase (splenomegaly). If it is not treated, *thalassaemia major* can lead to death before the patient reaches 20 years of age;

- minor and/or silent mutations of the gene of the beta globin chains in a homozygote or double heterozygous state, result in *thalassaemia intermedia*, the less severe form of the thalassaemias, that presents in an extremely wide variety of ways. Typical symptoms are anaemia, increased spleen size and biliary stones;

- the alteration of one copy of the gene (heterozygotes) of the beta globin chains leads to *beta-thalassaemia minor* that does not usually cause any symptoms or at least very mild symptoms (mild microcytic anaemia). People with this type of alteration are usually healthy carriers of the disease.

Alpha-thalassaemias. The *alpha-thalassaemias* are hereditary disorders characterised by reduced or suppressed production of the alpha globin chains. There are four human alpha globin genes. These are found in the following forms:

- the alterations of all four genes for the alpha globin chains leads to the serious condition of foetal hydrops. This is often lethal for the foetus or for the newborn infant immediately after birth.

However, immediate standard blood transfusions will allow the newborn child who survives to have a disease course through life similar to that of patients with beta-thalassaemia;

- in the so-called haemoglobin H disease, there is an alteration is due in three genes for the alpha globin chains and a microcytic anaemia is observed (low haemoglobin levels and small red blood cells) often associated with an enlarged spleen (splenomegaly). The disease usually presents during childhood or early adulthood;

- also in the case of *alpha-thalassaemia*, a mutation involving only one gene or only two of the four alpha genes results in *thalassaemia minor* (respectively of type 2 or type 1), the so-called 'silent' forms, without any symptoms at all.

When the diagnosis of a mild form becomes important: the case of delta thalassaemia.

From haematological point of view, the **delta-thalassaemia** is an innocuous condition since it involves the A2 haemoglobin (consisting of delta chains), that represents 2-3 % of the adult normal haemoglobin. Diagnosing the delta thalassaemia is however very important, because this can mask the diagnosis of the healthy carrier of beta-thalassaemia. In this last condition there is an increase of the Hb A2. However, if together with beta-thalassaemia there is also a mutation resulting from the presence of a delta thalassaemia, the value of Hb A2 will be reduced to normal levels, making the diagnosis of beta-thalassemia difficult.This is important for the genetic counseling because a child, born to parents who are both carriers of beta-thalassaemia, has one out of four possibility of inheriting the thalassaemia major, but if the HbA2 is normal that risk will not be recognised.

IS BLOOD TRANSFUSION STILL THE FIRST REMEDY FOR THALASSAEMIA?

TRUE. Appropriate transfusional therapy and the high safety standard of the blood products transfused are key factors of the therapeutic protocol of thalassaemia patients. It is useful to know when is the best moment for transfusion, the frequency and the amount of blood to transfuse, and what the related risks are.

Guidelines for choosing how much blood to transfuse

To raise the haemoglobin (Hb) level by 4 g/dl in a patient weighing 40 Kg and receiving AS-1 blood with a haematocrit of 60% would require 560 ml. This calculation assumes a blood volume of 70 ml/Kg of body weight.

	Haematocrit of Donor Red Cells			
1 g/dl	4.2 ml/kg	3.5 ml/kg	2.8 ml/kg	2.6 ml/kg
2 g/dl	8.4 ml/kg	7.0 ml/kg	5.6 ml/kg	5.2 ml/kg
3 g/dl	12.6 ml/kg	10.5 ml/kg	8.4 ml/kg	7.8 ml/kg
4 g/dl	16.8 ml/kg	14.0 ml/kg	11.2 ml/kg	10.4 ml/kg

Target increase in Hb level

When?

Transfusional therapy must only be started when the diagnosis of *thalassaemia major* has been confirmed through laboratory and genetic tests to identify the type of mutation. Early transfusion has progressively reduced and sometimes eliminated the clinical profiles seen in the past characterised by facial alterations, delay of growth, bone fractures and important extramedullary haematopoietic action (production of red blood cells in different sites to the bone marrow).

Frequency and Quantity

The amount of blood and the frequency of the transfusions depend on patient age and clinical condition, along with the target haemoglobin levels to be achieved. Current transfusion regimens aim to maintain pre-transfusional haemoglobin between 9 g/dl and 10.5 g/dl and to ensure that post-transfusional haemoglobin does not exceed 14-15 g/dl. This transfusion regimen allows normal growth, guarantees normal physical activity, adequately suppresses bone marrow activity and reduces the accumulation of iron from transfusion (iron overload).

Special graphs and formulas are available that allow clinicians to calculate the amount of blood to be transfused: this should not exceed 10-20 ml/kg, while in cardiopathic patients it should not exceed 5 ml/kg.

But what are the risks related to transfusions?

Transfusions can cause unwanted side effects that can have an important impact because they can worsen and cause some of the more serious 'complications' of thalassaemia, such as, for example, liver disease.

Infections: infections in thalassaemia syndromes can be caused by blood transfusions, by alterations in the mechanisms of immune response induced by hypersplenism, anaemia, iron overload and chelation therapy.

The most common serious viral infections are hepatitis B, hepatitis C, *Cytomegalovirus*, human immunodeficiency virus (HIV) and *Parvovirus B19*. These can cause a wide variety of pathologies such as infective megaloerythema or the 'fifth disease' in children, aplastic crises and myocarditis.

Bacterial agents include *Yersinia enterocolitica*, the virulence of which increases due to iron overload, just as with other bacteria such as *Klebsiella spp.*, *Escherichia coli*, *Streptoccocus pneumonia*, *Pseudomonas Aeruginosa* and *Listeria monocytogenes*.

Hepatitis B virus (HBV): in thalassaemia patients in many developing countries this is a significant cause of chronic hepatitis and of hepatocarcinoma (serious complications of chronic infection). The most common presentation is acute hepatitis with an incubation period of 4-20 weeks. In Western countries, most patients who carry the HBV virus are elderly and were infected before the introduction of specific virological tests on blood donors. Nevertheless, in developing countries, patients of all ages continue to become infected by HBV. The only therapy available for acute hepatitis B is support therapy while chronic hepatitis B patients who are candidates for therapy can be treated with pegylated interferon, nucleosides and nucleotide reverse transcription inhibitors (NRTIs) such as lamivudine, adefovir, entecavir and tenofovir.

Prevention of Hepatitis B

Vaccination programmes and the screening of blood donors, together with other public health measures have led to a significant reduction of the infection in most European countries, North America, and in other parts of the world. However, hepatitis B is still a serious health problem, especially in developing countries.

It should be remembered that HBV is transmitted vertically from mother to child. This means that if the mother is a carrier, a vaccine and specific anti-HBV immunoglobulin must be administered to the newborn infant within 12 hours of birth. This reduces the risk of transmission of the infection by over 90%. The best preventive strategy for hepatitis B is always prophylactic vaccination.

Hepatitis C (HCV)**:** so far, no vaccine has been developed for this virus. The active infection is diagnosed by the presence of HCV-RNA in the blood and HCV infection is one of the main causes of severe liver disease.The clinical course is extremely variable and determining factors are the severity, the chronic nature of the disease and response to treatment, and also include age, immune status, the specificity of the virus and co-morbidity.Standard therapy is based on the use of pegylated interferon and ribavirin (therapy that has also been approved for paediatric use); approximately 40-80% of patients respond to therapy.

In patients that fail to respond to therapy ('non-responders'), treatment options have not been clearly defined and are still considered experimental.

Cirrhosis: presentation in subjects with HCV is extremely variable. Liver cirrhosis is divided into three stages evaluated according to the Child-Pugh Score. The score (or points system) is widely used to evaluate the severity and prognosis of liver disease.

Score A: absence of ascites; bilirubin <1.5 mg %; albumin >3.5 g %; grade 0 encephalopathy.

Score B: treatable ascites; bilirubin 1.5-2.3 mg %; albumin 2.8-3.5 g %; grade 1-2 encephalopathy.

Score C: untreatable ascites; bilirubin >2.3 mg %; albumin <2.8 g %; grade 3-4 encephalopathy.

Hepatocellular carcinoma (HCC): can develop in 1-5% of subjects infected with HCV for at least 20 years, and is more likely to present after the development of cirrhosis, with an increase of 1-4% each year.

Prevention and early diagnosis of HCC are more efficient than attempts to treat the condition. This means that patients with cirrhosis must be checked every six months with liver echography and alpha-fetoprotein (a marker of liver tumour resulting from the increased regeneration of the liver cells) to identify the carcinoma as early as possible.

How can you protect yourself?

In order to avoid the risks associated with blood transfusions it is essential to always attend well-established and qualified transfusion centres and to avoid emergency transfusions. It should be remembered that now the majority of centres worldwide satisfy internationally stated safety criteria required by law, but some patients had received blood transfusions during the years in which there were still no such guarantees. These subjects require a more careful monitoring of possible negative consequences from transfusion.

ARE INFECTIONS THE MAIN COMPLICATION OF TRANSFUSIONAL THERAPY?

FALSE. Iron overload is one of the biggest problems related to blood transfusion. The iron contained in the transfused red blood cells is freed and if not removed can cause serious damages even to vital organs.

Iron overload

In physiological conditions, iron introduced with the transfusion is kept 'safe' because it is bound to a molecule such as transferrin. But in conditions of iron overload, transferrin can not bind all the iron and 'free' and 'non-transferrin bound iron' is formed (NTBI). This is toxic and can damage organ tissues, in particular, **liver**, **spleen**, **myocardium** and **endocrine organs**, with numerous clinical consequences, some severe, that can increase patient morbidity and mortality.

What are Free Radicals?

Free Radicals are chemical structures that are extremely reactive and that tend to cause particular damage to three cell components: the lipids, the proteins and the nucleic acids.

Toxicity of non-bound iron is in part due to the fact that it facilitates the production of free radicals that damage some cell structures (among which the mitochondrion, lysosomes and cell membranes).

Even if the organism prepares a series of defence mechanisms against the damage produced by free radicals, in patients with large iron deposits, these mechanisms are not able to function adequately.

In conclusion, since humans do not have a mechanism to eliminate excess iron, in cases of iron overload it is essential to use substances to remove the iron, i.e. an iron chelation therapy.

This means that iron chelation therapy is just as important as transfusion therapy in thalassaemia patients.

IS IRON OVERLOAD ONLY FOUND IN THE LIVER?

FALSE. Transfusion therapy, the main cause of iron overload in thalassaemia major, brings with it an increase in iron deposits in various organs and body tissues.

Accumulation of iron can involve all organs and can be distributed around the organism like 'leopard spots' (i.e. not uniformly), so organ-specific diagnostic tools need to be carefully used to identify it and allow it to be controlled.

The severity of the clinical profile will depend on the extent of the iron overloadon its duration and on the organs involved. The organs most frequently involved are liver, heart and endocrine organs.

Liver: iron overload in the liver typically presents with mild to moderate hepatomegaly. The main clinical characteristic of excessive iron deposits in the liver is fibrosis that can evolve into cirrhosis. In patients undergoing regular transfusions, portal fibrosis can present within 2 years of the first transfusion, while liver cirrhosis can develop within the first 10 years of life if the excess iron is not eliminated.

Transfusion iron overload

If not treated this becomes lethal in the second decade of life, usually due to the heart problems that result from it.

Heart: if the iron overload is not treated it can lead to complications that can impact on patient survival. Cardiomyopathy of iron overload is characterised by diastolic dysfunction with conserved systolic function in its early stages. Iron deposition in the myocardium is accompanied by hypertrophy and dilatation with degenerative phenomena and, more rarely, fibrosis. Symptomatic illness in general develops after 10 years after the start of transfusions. In the later stages, progressive heart failure can develop with seri-

ous systolic functional deficit and ventricular dilatation. The already compromised cardiac function can be worsened by transient myocarditis and pulmonary hypertension.

Rare cases of lesions typical of pseudoxanthoma elasticum (PXE) in thalassaemia patients

No correlation has been found with the severity of the haematological profile, Hb levels, the number of transfusions, the degree of haemosiderosis, chelation with deferoxamine.

Still little is known about the epidemiology, the etiopathogenesis and on the natural course of changes due to PXE in thalassaemia. But the presence of these lesions requires preventive strategies against the complications they can produce. PXE hits many organs and systems with microcalcifications in all the organs.

Endocrine organs: over time, iron overload can cause alterations in endocrine function. The most common alterations are:

- *Delay of growth*, due to growth hormone (GH) deficit, with a reduction in or complete absence of the production of this hormone by the hypophysis (or pituitary gland). The deficit in the production of growth hormone leads to small stature and slows down bone maturation. Growth is normal up to 9-10 years of age and then slows down. Diagnosis requires a regular and careful measurement of the rate of growth in height expressed in cm/year according to age and gender, and to the short height below the 3rd percentile for age and gender.

- *Hypothyroidism*, reduced capacity of the thyroid gland to produce the amount of thyroid hormones required by the organism. In cases of hypothyroidism, a delay of growth can be observed, a reduction in physical activity, dry skin and, in some cases, heart failure. It usually presents in the second decade of life and is rare in patients who are appropriately treated. Changes in thyroid function can be reversed at an early stage through iron chelation and good 'compliance' to treatment.

- *Hypoparathyroidism*, the reduced production of parathormone, is caused by hypocalcaemia and usually presents after 16 years of age.

- *Changes in glucose tolerance and diabetes mellitus*, include a group of metabolic disturbances that all present a persistent instability of glucose levels in the blood, ranging from hyperglycaemia (excessive amounts of glucose in the blood), and more frequently, to hypoglycaemia (low blood sugar levels). These can be the consequence of destruction of the pancreatic beta cells secondary to iron overload.

- *Delayed puberty/hypogonadism*, are the most frequent complications secondary to iron overload. Delayed puberty is defined as the complete absence of pubertal development in females at 13 years of age and in males at 14 years of age. Hypogonadism is defined in males as the absence of an increase in testicular volume and in females as the absence of mammary development at 16 years of age. Treatment depends on age, on the extent of the iron overload, of the damage to the hypothalamic-pituitary-gonadal axis, of chronic liver disease and on the presence of any psychological problems.

- *Osteopenia/osteoporosis*, are metabolic diseases of the skeleton characterised by a reduced bone mass and changes in the skeletal microarchitecture. The most common presentation is bone pain and pain in the spine , but patients can also be asymptomatic. Diagnosis is confirmed by bone densitometry. General treatment guidelines include administration of drugs, a correct life-style, physical exercise and diet.

IS IT TRUE THAT MONITORING IRON LEVELS IS VERY IMPORTANT?

TRUE. Continuous monitoring is needed to correctly evaluate the iron overload in order to set up efficient iron chelation programmes that are adequate for the specific needs of each patient.

The accurate evaluation of body iron overload is necessary not only to diagnose the accumulation of iron itself but also to efficiently manage the therapy. Both serological and instrumental tests are carried out.

The most common clinical serological test to evaluate iron levels in the organism is testing ferritin levels. This can be done by a quick screening test for iron overload that is sufficiently precise and non-invasive.

Ferritin and iron overload in the liver

Serum ferritin has a parallel course to intra-hepatic iron and is also a convenient and easy method to be used in the clinical practice.

Besides these obvious advantages, we should also consider that:

1) ferritin dosage is not always reliable because results can be influenced by a variety of factors, such as inflammation, an increase in body temperature, and hepatic alterations;

2) increased or decreased levels of ferritin do not correspond to the same increases or decreases in iron accumulated in the body tissues. There is certainly a good correlation with liver iron but not with cardiac iron.

There are a wide range of instrumental tests used to evaluate iron overload and its effects on function. Since most of the excess iron is deposited in the liver, the most common methods measure liver iron levels (LIC) and that are interpreted as accurate values of the concentration in the whole organism.

These methods include:

- **Liver Biopsy** (consisting of taking a sample of a small piece of the liver), was considered until recent years the only reliable method to measure intra-hepatic iron and to calculate the total amount of iron in the organism. More recently, biopsy has gradually been replaced by non-invasive methods and more closely correlated to deposits of cardiac iron, such as hepatic biomagnetic susceptometry by Superconducting QUantum Interference Device (SQUID) and magnetic resonance imaging (MRI). For patients with either diagnosed or a strong suspicion of iron overload, liver biopsy remains the most precise, sensitive and specific method to test concentrations of iron in the liver. Today, liver biopsy is carried out in optimal technical conditions, but it is still an invasive and painful procedure not without risks, although fortunately these are rare;

Magnetic Resonance in thalassaemia

Preliminary studies show an extremely high sensitivity and specificity also for low levels of iron deposits.

- the **Superconducting QUantum Interference Device** (SQUID) is an instrument that can measure even very small variations in magnetic flow, such as those provoked by iron stored in the form of ferritin in the organism. A more widespread use of this device has been limited by its high cost and by an imperfect correspondence with 'standard' results obtained by hepatic biopsy. Also, SQUID can not be used to measure cardiac iron.

- **Magnetic Resonance Imaging** (MRI) is a non-invasive technique that is extremely sensitive in evaluating the concentration and the distribution of iron in the whole organism. Following the numerous published reports that confirm its validity and reproducibility, it is becoming the most common technique used to monitor iron in the liver, cardiac iron and iron concentrations in other organs such as pancreas and the pituitary gland.

IS IT TRUE THAT MONITORING LIVER IRON IS ENOUGH TO MANAGE THALASSAEMIA?

FALSE. Since the patchy distribution of iron in the organism it is not enough to know iron levels in the liver. We also need to apply organ-specific monitoring.

To be able to carry out organ-specific monitoring, MRI is proving to be a reliable and efficient method and its use is becoming rapidly more widespread.

MRI in paediatric patients

MRI can also be used in paediatric patients because it has the advantages of high diagnostic resolution and non-invasiveness. Unlike other radiological methods (computed tomography or CT scan, conventional radiological methods, methods in nuclear medicine, etc.) the patient is not exposed to X-rays.

However, the patient must stay absolutely still in order to obtain a good image. This means that small children and babies must be given drugs to make them sleepy while the MRI is taken, and continuous monitoring during testing is essential.

To evaluate liver iron concentrations (LIC) using MRI, a method called the Ferriscan technique has recently been described. It has been registered both in the US and in Europe and it has shown good sensitivity and specificity, measuring LIC of 15 mg/g in dry liver tissue.

One particular advantage of this technique is the possibility to be used, after a short training period, in any centre that has a sufficiently up to date MRI equipment available.

Also the evaluation of myocardium iron levels with MRI has become increasingly more accessible through T2* testing.

T2* valueis obtained from images acquired by a standard MRI machine. The iron overload causes changes in the magnetic properties of the body tissues, that reduce the T2* values; T2* values in the body tissue decrease as iron concentration increases.

A less than 20 millisecond reduction in myocardial T2* values (that signals the increase of iron in the myocardium) is associated with a bigger reduction in left ventricular function.

The possibility of evaluating cardiac iron levels represents another way to stratify risk providing new diagnostically useful opportunities.

However, the factors that concern the risk of developing heart failure in conditions of myocardial iron overload are complex and are not only directly related to measurement of T2* levels.

OVER TIME, CAN THE IRON ACCUMULATED IN THE BODY TISSUES ALSO DECREASE ON ITS OWN?

FALSE. To decrease the excessive iron concentrations iron chelation therapy must be used. The aims of iron chelation therapy are to maintain safety levels of body iron and to provide a constant 24-hour protection from the toxic effects of iron.

Removal of iron from the organism: iron chelation therapy

The main objective of iron chelation therapy is to maintain body iron levels below toxic levels. The duration of therapy is more important than the dose, showing that it is essential to maximise the length of exposure to chelation therapy.

As mentioned above, the human body has active mechanisms of eliminating excess iron. Therefore, iron overload is an inevitable consequence of chronic transfusion therapy.

In order to eliminate this excess of iron from the organism, drugs able to bind to the metal present in the organism to form a 'chelate' are used, so losing the toxic effect of the metal and causing its excretion.

However, only a small part of the accumulated iron is available for iron chelation, so its removal is slow and only involves small quantities. In fact, a patient with iron overload needs months or years to reduce the body iron concentrations to safe levels even with the most intensive treatment.

According to current practice, iron chelation is started after the first 10-20 transfusions or when ferritin levels reach around 1,000 mg/dl.

During treatment, various vital parameters need to be monitored to evaluate the efficacy of the treatment and any onset of side effects.

The most important of these are serum ferritin, liver function, kidney function, an eye test and a hearing test, and tests to measure growth and development in children.

ARE ALL CHELATION THERAPIES THE SAME?

FALSE. The choice among different iron chelation drugs, in monotherapy or in combination, and the new techniques for a precise and non-invasive monitoring of iron levels in the organs. allow the administration of a customised therapy for each patient. The iron chelation therapy can be modified according to the type, the amount of iron accumulatedany complications that may occur, and quality of life.

Today, three drugs are available for iron chelation:

Deferoxamine (Desferal®)

Deferoxamine is a siderophore (iron transporter) capable of removing iron from ferritin, iron present in the liver and in the other organs, including the heart. The iron is excreted in the urine and the faeces.

The drug must be administered at sufficient doses to efficiently control liver and total body iron levels.

How to establish deferoxamine dosage

Ferritin levels can be used to establish the ideal dosage of deferoxamine for each patient, using this equation:

'Therapeutic Index' (TI) = average daily dose (mg/kg)/serum ferritin

The aim of iron chelation is to maintain the Therapeutic Index below 0.025.

Given the large size of the molecule, the standard recommended method is subcutaneous infusion for 8-12 hours of a solution at 10% deferoxamine, for a minimum of 5 nights a week, using an infusion pump.

The chelation process ceases immediately after suspension of drug infusion. If administered regularly and at adequate doses, treatment with deferoxamine has an excellent impact on survival and on complications related to iron overload in the heart and in other organs.

Furthermore, regular therapy improves patient survival and, if started before ten years of age, reduces the incidence of hypogonadism and other endocrine disturbances. The main disadvantage of the treatment is its parenteral administration.

Deferiprone

From its introduction into clinical practice, several studies have shown that the incidence of heart diseases caused by iron has been gradually reduced, with a key aspect represented by age of onset of the therapy.

Deferiprone (Ferriprox®)

Deferiprone was the first oral iron chelator authorised for clinical use able to chelate iron bound to transferrin, ferritin and hemosiderin, as well as to free iron.

This is a small molecule that is absorbed after oral administration (in tablet form or as a syrup, to be taken 3 times a day) and that is quickly metabolised in the liver through glucoronidation of one of the iron binding sites. The drug eliminates iron almost exclusively through the urine.

According to the European Medicines Agency (EMA), deferiprone can be used in second-line therapy in patients who are unable to receive deferoxamine. The EMA has, in fact, also recognised that deferiprone is more efficacious than deferoxamine in eliminating heart iron and its use has reduced cardiac-related mortality.

This information has been included in the documents issued by the EMA and in the information leaflet to make it available to patients.

The use of deferiprone in clinical practice has been consolidated over the years, confirming the favourable risk/benefit profile of this iron chelator.

Deferasirox (Exjade®)

Deferasirox is an iron chelator developed in recent years for oral use. Used once a day, it guarantees a chelation activity not inferior to those achieved with deferoxamine. It represents an option offering maximum comfort also when therapy must be started early in childhood.

The possibility of personalising therapy for each patient on the basis of the therapeutic objectives to be reached and the level of transfusion iron is an innovative aspect of deferasirox that is proving to be a model also for other chelators.

Combined treatment with Deferoxamine and Deferiprone

Deferoxamine and Deferiprone can be used as combination therapy in case of severe iron overload or when the result obtained with the use of one drug alone is not adequate for reasons of compliance or because of side effects. Deferiprone, being a 'small' molecule, is capable of entering into the organs and transporting the iron in the blood where it is passed to the deferoxamine and then eliminated from the organism. This process of iron transfer between these two drugs is called the 'shuttle effect'.

The two chelating agents can be administered in association (administration of the two drugs on the same day) or according to an alternate or sequential schedule (administration of the two drugs on different days).

The associated therapy provides 24 hours of exposure to iron chelation and, therefore, the theoretical advantage of offering 24-hour protection from the effects of labile iron.

On the other hand, this type of administration can also cause an increase in side effects.

Combined use is not currently included in the technical recommendations or on the information leaflet of the two drugs. It, therefore, represents an 'off-label' use that can only be applied under the direct responsibility of the doctor who prescribes it.

This depends on the fact that, in spite of the fact that the 'off-label' use is quite widespread ,above all in Italy, registrative studies necessary to evaluate the effects and risks of administration have not been carried out.

Only once such studies have been completed will we have precise information about recommended dosage, administration methods and the cases in which its use is to be preferred to standard therapy.

IS IT POSSIBLE TO SAY WHICH CHELATOR IS THE BEST?

FALSE. There is no such thing as the 'best chelator', but it is possible to know the characteristics of each of them, including their side effects, to be able to discuss the choice of the most suitable chelator with the doctor.

Deferoxamine

The most common side effects related to administration of deferoxamine include:

local skin reactions, including itching, skin rash and hardening of the skin, that can be due to an inadequate dilution of the drug. Intradermal infusion of the drug can cause ulcers at the infusion site.

Deferoxamine and microorganisms

Bacteria that can become virulent during therapy include: Yersinia enterocolitica that has on its external membrane a receptor capable of binding efficiently to deferoxamine. In this case, and in the case of fever in general, treatment should be temporarily suspended.

Another important consequence of administration of deferoxamine is the risk of infection from bacteria that use natural siderophores as a source of iron in order to become more virulent.

Overdosing in patients who do not have excessive deposits of iron can result in:

- Neurosensorial hearing deficit (if this is slight it is reversible), tinnitus and deafness (usually permanent), in particular in children with reduced iron overload. For this reason, is it recommended to carry out an annual audiometric monitoring.

- Eye disturbances such as night blindness, altered colour vision, reduced visual field, reduced visual acuity.

- Delay of growth, whose factor of risk is not only due to overdosage, but also to start age of the treatment (<3 years). The speed of growth improves when deferoxamine dosage is reduced. Bone lesions, such as rickets and genu valgum can be associated with metaphysary alterations, in particular in the vertebrae. Regular monitoring is needed to prevent such alterations, because these are irreversible.

Deferiprone

The most feared side effect is neutropenia (fall in neutrophil white blood cells to below 1500/mm3) that in the most severe cases can become agranulocytosis (reduction in the number of neutrophil granulocytes to below 500/mm3), whoseonset varies from few months to 9 years. During treatment with deferiprone, therefore, it is recommended to check white blood cell count on a weekly basis, above all in the first months of therapy, or more often if there are signs of infection, and concomitant treatment that reduces the number of white blood cells should be avoided.

Oral chelation and birth rates

In the recent years - there is a rise in the number of babies born with thalassaemia with respect to previous years. This increase is not due to a presumed failure of prevention policies, but it has been linked to an informed decision of the parents confident that today it is possible to live with thalassaemia maintaining a good state of health and a good quality of life. One of the decisive factors for this change in attitude has been the use of oral chelation therapy. These drugs increase patient compliance to therapy, improving its efficacy.

If there is serious neutropenia, the drug is suspended definitively and should not be restarted. This condition can be associated with thrombocytopenia.

Another side effect is arthropathy, that has a variable incidence. Symptoms range from non-progressive mild arthropathy, usually in the knees, to a serious erosive arthropathy (more rarely).

In some patients, a zinc deficit has been observed during therapy, especially in diabetics.

Deferasirox

The unwanted effects of deferasirox therapy include, above all, an increase in serum creatinine (36% of patients) that tends to resolve spontaneously

without reducing the dosage, gastrointestinal disturbances (15% of patients) that can reduce compliance to the drug, and skin rashes (11% of patients).

However, the worrying risk is the onset of kidney toxicity that has led both the US Food and Drug Administration (FDA, the US agency with competence for drugs) and the EMA to recommend carrying out specific urine/blood tests, above all in the first month of therapy, and then each month.

After its appearance on the market, there have been cases of liver failure, mainly involving patients with significant morbidity such as cirrhosis and cases of leukopenia, thrombocytopenia, pancytopenia or the worsening of these cytopenias if already present. In patients who develop cytopenia that is not attributable to any known cause, a decision should be taken whether or not to stop treatment.

DO ORAL IRON CHELATORS HAVE ANY ADVANTAGES OVER DESFERAL?

TRUE. Above all in terms of compliance and, therefore, determining an overall improvement in the patient's confidence in the therapy.

Oral chelators have completely changed the life of thalassaemic patients. As discussed above, the first oral chelator was deferiprone, in tablets or syrup, to be taken 3 times a day. The second was deferasirox, in liquid form to be taken once a day. Naturally, these drugs have the risk of possible specific side effects, as we have already seen, and for this reason, patients must be carefully monitored.

Their introduction in the treatment of thalassaemia has favoured a certain regularity in taking iron chelation therapy, leading to a substantial improvement in their survival, considering that inadequate compliance to iron chelator therapy represents one of the main risk factors for early death.

For this reason, compliance is a key factor, a phenomenon that can not be overlooked, if the objective is an efficient disease management from both a medical and a psychosocial point of view.

Oral chelators are also easier for the patient to manage on a daily basis. Just think about all the moving around the patient has to do, night time functions, etc., all of which need to be organised without interfering with a good chelation therapy.

Desferal: yes or no?

In spite of the advantages of oral chelators, the 'old' desferal (in subcutaneous or endovenous administration) still remains one of the most efficacious iron chelators if taken correctly and regularly. Adult patients who have found an optimal routine taking this drug should continue to do so.

CAN I TAKE ANY OF THE AVAILABLE IRON CHELATORS?

FALSE. The choice of the iron chelator depends on various factors, and among these, any possible side effects should always be taken into consideration.

The possibility of taking one iron chelator rather than another, having therefore a wider choice, such as with all drugs, is certainly an important advantage for the patient.

Also, the choice of the chelator is not casual but is the result of a medical decision based on clinical and scientific considerations, as well as 'getting to know' the patient better and gaining a better understanding of his or her individual needs.

Choice of therapy

The experience of each individual patient, in-depth discussed with the doctor, can be of fundamental importance in helping to choose the most suitable therapy, and modifying it according to patient needs and any complications there may be.

Therefore, the main criteria to consider in choosing the iron chelator are, on the one hand, its efficacy, long-term safety and the contraindications that can differ from patient to patient, and on the other hand, the preference of the individual patient together with the real feasibility of adhering to treatment.

Another key element is the amount of the different iron chelators to be used. In fact, the ability to calculate the amount of iron introduced with the blood transfusions has reached high levels of precision so today it is possible to establish exactly the most appropriated quantity of iron chelation therapy according to patient age and the accumulation of iron in relation to each individual chelator.

Therefore, the principal criteria to consider in choosing the iron chelator are efficacy, long-term safety and any contraindications.

CAN I TAKE A BIGGER DOSE IF I FORGET TO TAKE MY DAILY DOSE OR FORGET TO TAKE ALL OF IT?

FALSE. Because you would risk an overdose. If you forget you must contact your doctor or the hospital.

Iron chelators are most efficient if taken regularly without skipping the prescribed doses. In fact, the daily dose of deferasirox and the three daily doses of deferiprone guarantee a continuous and constant 24-hour chelator cover.

Deferasirox: if you forget to take the drug at the right time, you can take it at any other time within the same day. However, if you forget to take the daily dose completely you must not double the dose the next day.

Deferiprone: if you forget to take the drug at the right time, you can take it as soon as you remember and then continue with the next dose as usual. If you skip more than one dose, you must not take a double dose to compensate but you should continue your regular dose schedule.

Overdosage of Desferal

No-one intends to take an overdose, and it can lead to hypotension, tachycardia and gastrointestinal disturbances. There is no specific antidote. Administration of desferal must be stopped and suitable action taken to treat symptoms.

DO I HAVE TO STOP TAKING IRON CHELATION THERAPY DURING PREGNANCY?

FALSE. The question as to whether to stop iron chelation therapy depends on the type of drug taken and the need to remove iron from the body tissues.

Deferoxamine can be used during pregnancy. It should be stopped during the first trimester and then used in the second and third trimesters in patients with severe iron overload or at high risk of heart problems.

It has been demonstrated that it should not be administered during pregnancy in patients who do not have a serious iron overload and who had normal cardiac function before pregnancy.

Pregnancy and transfusion

During pregnancy the number of transfusions is increased to maintain the pre-transfusional haemoglobin levels to around 10 g/dL.

Deferiprone and deferasirox must, however, be stopped during pregnancy, and it is recommended the use of a reliable contraception method while taking these drugs.

WILL THERE BE ANY COMPLICATIONS IF I DON'T TAKE ANY IRON CHELATOR OR IF I STOP TAKING IT?

TRUE. Iron overload secondary to transfusion therapy is one of the main factors in the etiopathogenesis of various complications in thalassaemic patients.

Chelators only guarantee their beneficial effects if they are used continuously, because not taking them or stopping taking them would mean that excess iron is not removed from the organism and this would lead to complications, as described above.

It should always be remembered that being able to follow the treatment schedule precisely (adherence to treatment or compliance) is the main reason for the reduction in mortality and in all the complications related to thalassaemia!

Adherence to treatment or compliance

Adherence to treatment is one of the main problems for doctors and patients. Failure of therapies is due not so much to the lack of protection from the drug as to the fact that the patient cannot maintain an adequate adhesion to the therapeutic regimen. The patient must be encouraged to follow the treatment programme. The disease prognosis depends on a continue and regular taking of the iron chelation therapy.

DO PATIENTS NEED REGULAR MONITORING FOR COMPLICATIONS?

TRUE. All patients with thalassaemia must undergo regular clinical tests to evaluate disease status in order to prevent complications of iron overload.

Hepatitis C: patients must undergo tests if there is confirmation of HCV-RNA presence, moderately increased ALT levels and abnormal liver histology.

Hepatitis B: patients must undergo tests if there is confirmation of HBV presence and increased transaminase levels.

Cardiopathies: it is important that patients are constantly monitored even in the absence of clinical signs, to be able to immediately identify any changes in cardiac function and to start appropriate therapy.Well-chelated patients must firstly be evaluated at puberty, followed by annual check ups. Asymptomatic patients with some evidence of heart failure must be checked every 3-6 months.

Delay of growth: must be evaluated in patients with reduced growth rate.

Hypothyroidism: thyroid function must be checked every year from the age of 12 years.

Hypoparathyroidism: tests include calcaemia, phosphorus levels and phosphate balance to be carried out from 16 years of age.

Alterations in glucose tolerance and diabetes mellitus: patients over the age of 11 years must undergo 6-monthly or annual tests.

Pubertal delay/hypogonadism: girls over the age of 13 years and boys over the age of 14 years with absent/interrupted pubertal development should undergo tests.

Osteopenia/osteoporosis: these should be tested in hypogonadic patients, diabetics, hypothyroidic and hypoparathyroidic patients, and patients with symptoms of pain.

I SOMETIMES HAVE TO TAKE OTHER DRUGS BESIDE IRON CHELATORS ARE THESE REALLY NECESSARY?

TRUE. If there are any complications due to iron overload, an overall therapeutic strategy is needed with specific treatment to limit damages deriving from the onset of other pathologies.

Cardiopathies. Intensive chelation is essential to quickly neutralise iron toxicity and remove iron deposits. Over recent years, patients with moderate ventricular dysfunction are treated with drugs that improve myocardial function, such as angiotensin converting enzymes (ACE inhibitors).

Other drugs that can be used are:

- **Digoxin**. This should not be used in the first stages of cardiomyopathy, but can have a specific role in maintaining satisfactory heart frequency in patients with stable atrial fibrillation.

- **Beta blockers**. These are introduced with caution if the cardiac disease has stabilised.

- **Diuretics**. To be used with caution controlling kidney function.

- **Anticoagulants**. They are used in patients with central venous catheters, or affected by chronic atrial fibrillation, to prevent the potentially fatal complication of the formation of intraatrial thrombus with embolisation and development of pulmonary hypertension.

Controlling complications of iron overload

In recent years there has been a great progress in controlling the complications of iron overload in thalassaemic syndromes, thanks also to the close collaboration among doctors of different disciplines.

Hypothyroidism. The treatment depends on the seriousness of the disease. In its symptomatic form, L-tirosine is used while the treatment of pre-clinical or compensated hypothyroidism is intensified with chelation therapy and, if needed, with administration of small doses of L-tirosine.

Hypoparathyroidism. Therapy is based on the oral administration of vitamin D or analogues. Calcaemia must be carefully monitored, because hypercalcaemia can be a common complication. Use of a phosphorus chelator (without aluminium) can be considered in patients with persistent hyperphosphoremia. Tetany and cardiovascular symptoms due to serious hypocalcaemia require endovenous administration of calcium and oral vitamin D.

Changes in glucose tolerance. This can be improved by a diet with reduced carbohydrate intake, by losing weight, and by intensive chelation therapy. Symptomatic patients require insulin therapy.

Delay of growth. Besides being associated with iron overload, it should be remembered that deferoxamine is an important cause of delay of growth. Therapy consists of administration of growth hormones, integrated with zinc sulphate in patients with low zinc levels.

Pubertal delay/hypogonadism. In girls, oral ethinyl estradiol is recommended, while boys should receive once monthly intramuscular depo-testosterone. It should be remembered that also these treatments have multiple associated complications, so each patient should be evaluated individually.

Osteopenia/osteoporosis. There are no well-codified protocols for the therapeutic treatment of these complications. The following aspects should be considered: maintaining adequate pre-transfusion haemoglobin (Hb) levels, integrating oral calcium, substituting therapy with sex steroids (patients with hypogonadism) and with biphosphonates.

IS IT TRUE THAT A HEALTHY LIFESTYLE CAN EXERT A SYNERGIC EFFECT ON THE THERAPY?

TRUE. Besides the iron chelation therapy for iron overload from transfusion dependency, patients can follow some daily reccomendations to improve their quality of life.

Nutrition

It is not usually necessary to follow a particular diet except in cases in which there are specific prescriptions. During the growing period, an adequate calorie intake is recommended with a good balance of fats and sugars.

During adolescence and in adulthood, it could be useful to follow a diet low in carbohydrates to prevent or delay any onset of a reduced tolerance to glucose or of diabetes.

Vitamin E

Vitamin E requirements are high in thalassaemia, the efficiency and the safety of its consumption have not been formally demonstrated and Vitamin E supplements are not currently recommended for use in these patients.

The increased absorption of gastrointestinal iron is characteristic of thalassaemia, so a reduction in the absorption of iron intake from the diet through consumption of food products with a low iron content could be helpful for thalassaemic subjects.

Iron is present in most food products. However, the diet can be modified by privileging those foods that reduce absorption with respect to those that increase it:

foods rich in calcium, like milk and cheese products, can reduce iron absorption, so it is a good idea to have a daily intake of milk. This is also useful in preventing osteoporosis.

Also cereals reduce iron absorption in the gastrointestinal tract and counterbalance the effect of vitamin C that instead increases absorption.

Supportive care

The administration of supplements must be carried out with particular care under continuous monitoring to prevent toxic effects.

Calcium: in thalassaemic subjects various factors lead to a loss of calcium, and calcium supplements must only be given according a precise indication. Vitamin D can be administered to balance calcium levels, especially if hypothyroidism is presented.

Folic acid: thalassaemic patients who are not transfused or who have a low transfusion demand have increased consumption of folates and can develop a folate deficit. If necessary, folic acid supplements can be prescribed (1 mg/die).

Vitamin C: iron overload causes a higher percentage of oxidation of vitamin C and some patients have a vitamin C deficit. Vitamin C increases the amount of iron available for chelation and so increases the efficiency of deferoxamine. However, it also increases the gastrointestinal absorption of iron and, therefore, increases toxicity. Because of this, patients receiving deferoxamine should only take vitamin C supplements when absolutely necessary. It is a good idea to avoid drugs such as aspirin or throat tablets, and certain nutricentric foods containing vitamin C.

Zinc: during chelation therapy a zinc deficit can sometimes be observed. Zinc supplements should, however, only be administered under strict clinical and laboratory monitoring.

Abusive substances

Alcohol: thalassaemic patients should be discouraged to drink alcohol because it can increase the oxidative damage of iron and aggravate effects of the hepatitis virus on liver tissue. The contemporary presence of these three factors increases the probability of developing cirrhosis and hepatocarcinoma. The excessive use of alcohol also reduces bone formation and this represents a risk factor for osteoporosis. Also, the interaction between alcohol and various drugs

must not be underestimated.

Smoking: cigarette smoke can have a direct negative effect on bone remodelling (associated with osteoporosis) and has numerous harmful effects on health in general.

Drug abuse: in many countries, the use of drugs is common among adolescents and young adults, but for somebody with a chronic disease this can be a serious danger for a condition that is already compromised, upsetting the delicate balance between those factors that regulate physical and mental health.

Medical staff must help the patient keep this in mind, taking into consideration the challenges that adolescents have to face as they grow up. There is the risk that, as for every adolescent, taking drugs is seen as a way to change both the way they behave and also the way they are seen by others.

For a young person with any form of chronic illness, a sense of dependency, diversity and anxiety can lead them to look for 'normality' through drug abuse.

Sport

Generally speaking, physical activity must always be encouraged and there is no reason why a thalassaemic patient should not take part in sport, within the limits of his or her interests and ability, unless there is a precise medical indication not to do so.

Conditions that require particular attention are:

- splenomegaly (avoid sports with risk of abdominal trauma)

- cardiopathies (moderate the physical activity)

- osteoporosis (avoid contact sports that present a risk of fracture).

IS IT TRUE THAT THALASSAEMIC PATIENTS SHOULDN'T HAVE CHILDREN?

FALSE. The improvement in therapeutic protocols in industrialised countries means that today thalassaemic patients CAN have children.

The obstacles to parenthood for both men and women were the absence or delay in sexual development, a cause of particular frustration in patients, and the possible transmission of viral infection. Today, these obstacles have for the most part been overcome. However, the problem of family planning remains, since it is important to plan the pregnancy in such a way as to avoid any situation that could put mother and child at risk.

The haematologist and the obstetrician-gynaecologist must work close together in order to best manage the pregnancy.

Pregnancy and risks

Pregnancy does not change the natural course of thalassaemia. The biggest risks are those associated with an increase in the possibility that there is a delay of foetal growth and of a premature birth.

CAN WE AVOID GIVING BIRTH TO A THALASSAEMIC CHILD?

TRUE. Prevention can be promoted by a thalassaemia screening programme as part of every national preventive initiative from puberty, before pregnancy or at the beginning of the pregnancy.

Existing prevention programmes in Italy have already achieved great results in the past. Since we live in a country in which thalassaemia is endemic, in order to be really effective, these programmes must be extended to all young people, with widespread screening not only of couples at risk.

Some figures… to give us an idea

Around 300,000-500,000 babies affected by thalassaemia are born in the world every year, and this number is still too high. For this reason, there is still a lot to do to improve prevention strategies, particularly in developing countries.

On the other hand, if a couple want to have children, and one or both of their parents suffers from thalassaemia or is a carrier, they must first of all be informed of the risk of their child having the disease. The couple must also be informed on the possibility of prenatal diagnosis, an important part of the prevention programme that allows the couple to decide whether to continue or interrupt the pregnancy .

The diagnosis of thalassaemia before the birth of the foetus can be made by a biopsy of the chorionic villi, amniocentesis, cordocentesis or with the innovative method of culdocentesis.

The choice of the type of test depends on the stage of the pregnancy and on the results of a preliminary evaluation of the parents.

The biopsy of the chorionic villi can be carried out very early in the pregnancy, i.e. from the 10th week. A DNA sample taken from the placenta can be analysed to evaluate the presence of genetic mutations.

The **amniocentesis** is a procedure that is carried out after the 15th week of pregnancy. A sample of amniotic liquid is taken from the uterine cavity using a thin needle inserted into the mother's abdomen.

The **cordocentesis** is an ecographically-guided examination that takes a sample of some drops of cord blood using a very thin needle that does not enter into contact with the foetus. The cordocentesis can be carried out between the 8th and the 22nd week of pregnancy.

The **culdocentesis** is a new prenatal diagnostic test that has been shown to already give reliable results from the 2nd month of pregnancy, i.e. one month before the villocentesis. This is the main, but not the only, advantage. A sample is taken of liquid from the coelom and this contains foetal cells. The sample is taken transvaginally without any need to perforate the amniotic sac or the placenta, and this means there is less risk of causing foetal malformation.

Culdocentesis

This test provides an early diagnosis that allows the couple to choose whether or not to proceed with the pregnancy. The couple may choose a voluntary interruption of the pregnancy (VIP) rather than a therapeutic abortion, with some benefits, both physical and emotional, for the woman.

ARE THERE ANY STUDIES ABOUT THE POSSIBILITY OF INTERVENING ON A FOETUS AFFECTED BY THALASSAEMIA?

TRUE. There is a very promising line of research that could lead to a big step forward in the prenatal therapy for thalassaemia.

'In utero' transplant is a technique by which stem cells are infused into the umbilical cord to 'correct' the thalassaemia while the foetus is still in the womb.

Support research!

More research is needed so that a child born with thalassaemia can be cured in his or her lifetime. We need your support!

Various protocols are currently used and recent studies have confirmed the grafting of paternal stem cells transplanted in a foetus affected by thalassaemia during the 2nd trimester of pregnancy.

IS THERE A CURE FOR THALASSAEMIA?

TRUE. Transplantation of bone marrow stem cells in children or very young patients allows up to 90% of patients to be considered cured. Also the results obtained with transplantation of cells from non-sibling donors or using cord blood cells are encouraging. Results are only compromised by those patients transplanted as adults who still have a high risk that the disease will represent itself.

Bone marrow transplantation for thalassaemia must be considered for very young patients or before complications due to significant iron overload arise.

The doctor, the patient and his or her family must, however, weigh up the relative advantages and disadvantages of the transplant procedure with those of conventional therapy.

The possibility of performing a bone marrow transplant is related to the availability of a compatible related or unrelated donor.

Some figures...

Since 1981, over 1.500 bone marrow transplants have been carried out worldwide.

Three classes of patients have been identified on the basis of three risk factors: inadequate iron chelation therapy, the presence of hepatic fibrosis, hepatomegaly.

These factors have an extremely important impact on the post-transplant result. Patients in 'Class I' have no risk factors. Patients in 'Class II' have one or two. Patients in 'Class III' have all three risk factors.

The clinical follow up after bone marrow transplantation is particularly important. During the first year, haematological parameters must be carefully monitored to evaluate grafting, infectious complications and graft-versus-host disease.

ARE THERE ANY OTHER 'NON-PHARMACOLOGICAL' THERAPIES BESIDES BONE MARROW TRANSPLANTATION?

TRUE. Cord-blood transplant. This technique offers various advantages over bone marrow transplant. Its use has led to a big reduction in mortality rates but there has been an increase in the possibility lack of grafting and representation of the disease.

...more figures

So far, around 6.000 transplants have been performed worldwide using stem cells from cord blood. The first transplant was performed in Paris in 1988 on a boy affected by a severe form of anaemia. Stem cells were taken from the umbilical cord of his mother's second pregnancy.

A type of transplant that has aroused great interest in recent years is that using stem cells obtained from blood in the umbilical cord at birth.

This technique has several advantages, including having a wider pool of donors and the easy collection procedure of stem cells at birth, nearly always a sufficient amount for a valid donation. This avoids having to wait for a suitable donor to be found

AND DOES PHARMACOLOGICAL RESEARCH OFFER ANY HOPES FOR THE FUTURE?

TRUE. Among the 'experimental' therapies we find pharmacological approaches using bland chemotherapeutics, substances that act on the cell cycle and slow down or even interrupt it, and that activate foetal haemoglobin synthesis.

One of the most used drugs in experimental studies is hydroxyurea, a drug studied for many years in cases of polycythaemia vera and in chronic myeloid leukaemia, without serious side effects.

Hydroxyurea is now established as the drug of choice for falciform anaemia and thalassodrepanocytosis, diseases in which it achieves a big reduction in the number of vaso-occlusive crisis.

Results obtained with hydroxyurea in thalassaemia intermedia and *thalassaemia major* have not always been optimal.

The only drug that achieves a big increase in haemoglobin levels is deoxy azacytidine, but very long-term use can cause cancer.

Hydroxyurea

This probably does not achieve the same positive results shown in drepanocytosis because most thalassaemia patients are transfusion dependent. Frequent transfusions lower or suppress endogenous erythropoiesis, particularly in those cells that respond to hydroxyurea.

CAN GENE THERAPY CREATE A WORLD WITHOUT THALASSAEMIA?

TRUE. The scientific progress and the success achieved in finding a cure for thalassaemia represent a real chance for a future without this disease. However, more studies are still needed to evaluate efficacy and safety.

Is gene therapy the treatment of the future?

Two patients with beta-thalassaemia major were treated at the end of 2006. It's still too early to say whether the expected benefits have been achieved.

Red blood cells are continuously produced by haematopoietic stem cells in the bone marrow. Therefore, stable transfer of a normal copy of a beta globin from a 'normal' couple into patient's stem cells through gene therapy would lead to a life-time production of normal red blood cells.

GLOSSARY

APLASTIC CRISES: suspension of the productive process of the bone marrow that provokes a strong reduction or the disappearance of all the bone marrow elements (red blood cells, white blood cells, and platelets) or also only of red blood cells, resulting in anaemia.

ARTHROPATHY: a disease of the general articulation, both inflammatory (arthritis) and degenerative (arthrosis).

BETA-BLOCKERS: drugs that block the electrical nerve impulses that stimulate the heart, reducing cardiac activity.

CARDIOMYOPATHY (or myocardiopathy): a disease of the heart muscle, that can be primitive (essential, due to unknown causes) or secondary to various causes (infective, from an accumulation of toxic substances such as iron, due to general disease status such as hypertension, diabetes, obesity, etc.).

CELLULAR MEMBRANE: complex structure that delimits the cell.

CIRRHOSIS AND HEPATIC FIBROSIS: disease of the liver consisting in a progressive degeneration of hepatic cells, with increased volume and connective hardening of the connective tissue that lies between the cells (fibrosis) and its subsequent retraction. This results in serious organ structural changes, with the organ becoming deformed, hardening and atrophying.

COLLAGEN: a protein that forms the support and connective organ structures (connective tissue), such as for example, tendons, cartilage, ligaments, bone organ matrix, etc.

CYTOPENIA: reduction in the number of bone marrow or blood cells.

DIASTOLIC: dilation phase of the heart cavity, both atrial and ventricular.

DIASTOLIC DYSFUNCTION: abnormality of the cardiac filling (during the diastolic phase).

DIURETICS: substances that favour diuresis (excretion of urine).

DYSPNEA: permanent or occasional difficulty in breathing due to a restriction in the respiratory apparatus with obstacles to air circulation or to a disease of nervous origin or due to toxic infection.

EPISTASIS: light or heavy bleeding from the nose. This can be a single or a repeated event due to local (congestion or erosion of the mucosa, trauma, etc.) or general (defective coagulation for genetic reasons or due to hypertension, infection) causes.

FOLLOW UP: an overall term used to indicate the clinical and laboratory tests and examinations that are carried out for a certain length of time in order to evaluate the disease course or the efficacy of a therapy.

GLUCURONIDATION (or glucoronation): enzymatic reaction that occurs in the liver in which drugs or exogenous or endogenous toxic substances are combined with glucuronic acid to form inactive products and be more easily eliminated by the kidneys (through urines) or by the liver (throughbile).

HCV-RNA: most sensitive indicator to identify people infected by herpesvirus C, that demonstrates the presence of the RNA of the virus through a laboratory procedure called polymerase chain reaction (PCR). HCV-RNA can already be revealed just a few days after exposure to the virus, well before any manifestation of antibodies.

HEART FAILURE: symptomatic myocardial dysfunction that provokes a defined model of haemodynamic, renal and neuro-hormonal compensatory response. The myocardium is unable to guarantee the cardiac workload required by the organism with a consequent reduction in transport of blood to the tissues and venous pooling in the pulmonary and systemic circulation. Clinical manifestations can reflect a left or right ventricular dysfunction (deficit).

HEPATOMEGALY: an increase in liver volume, a symptom of disease of the liver or of some other system or apparatus (heart failure, leukaemias, etc.), or of infective disease (viral hepatitis, malaria, typhoid and others).

HETEROZYGOUS: genetic condition of a cell or of an organism consisting in the presence of a couple of different alleles for a given gene.

HISTOLOGY: a discipline that entails the microscopic and submicroscopic study of the structure of living material, and in particular, tissue organisation and function.

HOMOZYGOUS: condition characterised by the presence of parts of DNA/RNA that are identical at specific points (loci) corresponding to a couple of chromosomes.

HYPERSPLENISM: syndrome characterised by an increase in spleen size, primitive (due to unknown causes) or secondary to various bone marrow diseases.

IDROPE FETALE: syndrome that occurs in the foetus characterised by a large retention of fluids (oedema). Can occur in the presence of a serious form of haemolytic anaemia (e.g. alpha-thalassaemia, Rh factor incompatibility).

IMMUNOGLOBULIN: family of proteins characterised by their molecular structure, including molecules that are part of the immune defence mechanism (antibodies).

INFECTIVE MEGALOERYTHEMA: infective erythema or 'fifth disease', a benign childhood exanthematic disease caused by human Paravirus B19. It starts with an intense erythema (redness) to the cheeks, without fever, extending to the arms and the legs. The erythema usually fades in 1-2 days. The disease can have articular complications (arthritis and arthralgia).

LYSOZOME: organelle found inside a cell able to hydrolyse nearly all biological macromolecules.

MITOCHONDRION: organelle contained in the cytoplasm of each cell. It contains important enzymatic systems that represent the energy source for the cell.

MYOCARDITIS: inflammatory process of the myocardium. It can be caused by an infection (above all of the upper respiratory tract, tonsils and teeth) but also by rheumatic disease, ionising radiation, chemical or physical agents, pharmacological products. In most cases, initial clinical manifestations are aspecific. The speed of diagnosis (clinical and laboratory) and adequate therapy are fundamental to disease course. In most cases, the disease is resolved in 4-6- weeks.

PLASMA HALF-LIFE: a parameter that indicates the time needed to verify that the amount of drug in the blood has been reduced by half.

SCREENING: term used to indicate the examination of a large number of basic units of the same type (individuals in a population, events, etc.) to look for those with a particular characteristic or quality.

SPENOMEGALY: increased spleen size.

SYSTOLIC FUNCTION: rhythmic contraction of the muscles of the atriums and the ventricles of the heart that is repeated alternatively during cardiac function.

THROMBOCYTOPENIA: fewer than 100,000/mm3 platelets in the blood.

TRANSFERRIN: glycoprotein capable of 'capturing' iron (such as that, for example, from food, absorbed by the intestinal mucosa and that from red blood cells, after the dissolution of red blood cells) and to transport it through the circulation towards vascularised tissues (above all, to the bone marrow) where it is deposited so that the iron can bind in specific points (receptors) to the erythroblast membrane.

FONDAZIONE
PER LA RICERCA FARMACOLOGICA
GIANNI BENZI
ONLUS

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DEEP DEFERIPRONE EVALUATION IN PAEDIATRICS

Through these pages we hope to have given you some information to live better with thalassemia, understand its therapy and avoid complications!

But in the end, what can I say?
I am learning how to live, just like everybody else.
(Andrea Mucciolo)

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