Current experimental approaches include the use of less toxic non-myeloablative transplants, the use of unrelated matched donors, and the use of related haploidentical donors. These are curative interventions, but are only ethically justifiable where drugs are ineffective given current knowledge. More research is needed to improve safety of these procedures.

Gene therapy has been under investigation for a number of years. This is a long process (gene therapy for SCID was initiated about 15 years ago). Currently, gene therapy for β-thalassemia has reached preclinical studies. A single patient has been treated with success, but with a caveat that some potentially dangerous cells have also appeared. Using a different viral vector (named GLOBE), under development at TIGET (a centre able to offer bone marrow transplants and other interventions necessary in order to give patients choice and ensure consent is real), an Italian group under Dr Giuliana Ferrari have demonstrated that correction of β-globin synthesis can be achieved in mice, thus correcting chain imbalance and ineffective erythropoiesis.

Another group from the USA, presented by Dr Stefano Rivella, have identified a possible difficulty in gene transfer when there is a β+ mutation involved (such as the IVSI-110 mutation which is common in the Mediterranean populations) in that the messenger RNA in this case is stable, limiting the translation of the of the transgenic transcripts. The group has developed a new lentiviral vector (AnkT9W) with an 'Ankyrin' sequence, which increases the β-globin mRNA during red cell maturation, improving the phenotype of the mice. All this shows that gene therapy is progressing and may in a few years reach the patients as an effective and safe therapeutic approach.

In addition to the development of advanced therapies there are a number of positive developments in prospect, using conventional pharmaceuticals derived from naturally occurring substances which aim to increase fetal haemoglobin production and improve the clinical outcome of thalasaemia. What?

The need to sustain innovation through the support and promotion of research, and facilitating positive outcomes throughout the development process of therapies towards regulatory approval into clinical use will require long-term strategic support from all key stakeholders: patients, academics, clinicians, industry, regulators and policy-makers if those at risk are ultimately to benefit.

# Compliance, adherence, concordance – what's in a word, and does it matter?

**Compliance, or adherence, by patients to prescribed therapies is an important aspect of patient care that directly affects health outcomes. The topic is of particular relevance in thalassaemia, where adherence to treatment, especially iron chelation, has a direct impact on survival. For this reason, TIF decided to include presentations from both sides of the patient-doctor relationship in the programme of the 2nd Pan-European Conference on Haemoglobinopathies. We thank both speakers, Dr Chris Sotirellis and Dr Antonio Piga, for their interesting contributions to the debate.**

*Chris Sotirellis with his airplane (he is a certified pilot)*

## The patient's perspective:

### Dr Chris Sotirellis, Vice-President, UK Thalassaemia Society

Dr Chris Sotirellis is an aeronautical engineer by profession, and the Vice-President of the UK Thalassaemia Society. He pointed out that adherence to medication has been a big problem since the time of Hippocrates, who wrote that patients often lied about taking their medication. In modern days, the terminology describing the phenomenon of "taking medication as prescribed" has a significant effect on patients' attitudes.

### From compliance to adherence

Compliance, the term traditionally used, refers to "the extent to which the patient's behaviour matches the recommendations from the prescriber". It implies submission or involuntary conformity: "Comply or else...". It implies passivity on the part of the patient, who, if not compliant, is seen as a rebel, incompetent, or a nuisance. In this approach, the patient's beliefs are not interacting with the doctor's, or they are seen as an obstacle to treatment. The higher status of the doctor in relation to the patient is implicit.

The term compliance has now largely been replaced by adherence. Adherence refers to "the extent to which the patient's behaviour matches agreed recommendations from the prescriber". It evokes a sense of being closely attached to a set regimen, following the rules, guidelines or standards. However, adherence implies a more active role than compliance: a collaboration with the physician and a self-motivated decision to adhere to advice. In this model, patient

acceptance is based on trust and agreement is part of the process.

**The next level: concordance**

According to the Royal Pharmaceutical Society of Great Britain (1997) – there are two sets of equally cogent health beliefs – that of the patient and that of the doctor. The patient should convey his/her health beliefs to the doctor, and the doctor should enable this to happen. "The intention is to assist the patient to make as informed a choice as possible about the diagnosis and treatment, about benefit and risk and to take full part in a therapeutic alliance. Although reciprocal, this is an alliance in which the most important determinations are agreed to be those made by the patient".

This leads to the concept of concordance. Concordance is not synonymous with either compliance or adherence. It is based on the notion that consultations between clinicians and patients are a negotiation between equals, and acknowledges that individual patients may differ in their evaluation of the risks and benefits of a particular medicine. Health professionals are concerned on the quality of their prescribing, aiming at the best possible clinical outcomes. At the same time they are urged to be patient-centered and evidence-based. Yet these two can conflict.

**Reasons for non-adherence**

Thalassaemia patients are asked to comply with many treatments, including blood transfusions, chelation, treatments for hepatitis, bone disease, diabetes, heart, hormones, etc. It can feel as if life is reduced to "getting treatment". There is a need to respect the patient's "normal life" priorities and the patient's time to fulfil them. Do even so-called centres of excellence respect these needs, for example by providing after-hours transfusion with proper staffing and other support to minimise hospital visits? Is there a willingness to work with the patient? The patient can easily be marginalised and seen as a burden to society, yet with the right care he/she can contribute enormously to society.

Non-adherence can be intentional or involuntary. It may relate to the quality of information (clarity, evidence, source), the impact of the regimen on daily life (costly, painful), the physical and mental capacity of the patient, or his/her social isolation, his/her ability to absorb more of the burden of uncertainty and treatment, or his/her self-image. The treatment offered cannot be predicated solely on the doctor's views, but also by an understanding of the real burden on the patient's life. This understanding comes by "listening" to the patient, and not keeping everything on a clinical level.

**What patients expect from their doctors**

Patients with chronic conditions use reasoning and judgement to make decisions. In doing so, they must grapple with irreducible uncertainty concerning their life, including its duration and its content (career, having a family, paying off a mortgage, etc.). Medical practitioners often ignore these long-term goals and the uncertainties that affect the daily lives of patients. Yet the practitioner is the only "buffer" the patient has between science, the health services and the pharmaceutical industry. This is the real privilege doctors have, and their power and status derives from it, so they should value it and use it wisely. The doctor's motivation should always be clear in seeking the optimum for their patients and in their role of buffer between the patient, services and industry.

Environmental and social factors which influence the patient include the interpersonal relationship between the doctor and patient, as well as the quality of support from family members and friends. Most patients intuitively know their doctor's attitude and willingness to understand these things. The patient requires respect for his/her time, respect for the priorities of his/her life, and honesty on the part of the doctor. The patient hopes that the doctor will get out of her/his routine in order to help, accepting the patient's "good" and "bad" days, their fears and uncertainties. The patient expects the doctor to share in these battles and be an ally, helping to reduce the burden of the disease and the treatment. Chris says: "The doctor must accept that I am more than just a thalassaemia patient: I am just as complex a being (if not more complex) than she/he is!"

Everyone wants to know what's going on in gene therapy...

... so starting with the next issue,
TIF Magazine will bring you a regular update
on the latest research and developments,
compiled by some of the top experts in the field.

"Gene Therapy Update" - starting with issue 58!