Position paper 5.6  

Chronic Hepatitis C in transfusion depended thalassaemia  
The view of the Global Patient Community

Introduction
In the last two decades, the development of Guidelines by international experts for the management of β-thalassaemia major has contributed immensely to the better definition, not only of the two basic arms of the medical care of this disease i.e. that of blood transfusion and iron chelation, but also of the multidisciplinary care essential to address effectively the medical complications associated with such a polyorganic chronic disease. In countries where such medical care is established and provided in the context of national health services (systems) coupled with effective prevention strategies, the survival and quality of life of patients with this disease over the years have dramatically improved. In these, albeit relatively few countries, as compared to the global magnitude of the problem, one can safely state that the natural history of this previously considered fatal genetic childhood disease has been literally completely reversed and that the pooled knowledge and experience from these countries, have paved the way towards the better recognition of those components essential to comprise an effective strategy for its control.

Unfortunately and despite the fact that WHO adopted two resolutions through its Executive Board and World Health Assembly (WHA) in 2006 specifically on Hb disorders, one for thalassaemia (Res. EB118.R1), and one for SCD (Res.WHA59.20) the current status of programmes for their control (prevention and management) is widely heterogeneous across the world, and TIF’s efforts and activities towards supporting the development of such programmes consequently vary considerably between and within regions and countries.

Unfortunately to date despite the huge advances in the knowledge of the pathophysiology, progression, prevention and management of these disorders, accurate epidemiological data are still needed in many parts of the world, preventing the appropriate assessment of their real contribution to the global disease burden – a prerequisite for their inclusion as prioritise on national and global health agendas. However, the work of the EU on Rare Diseases (RD) and WHO on Non Communicable Diseases (NCD) and despite the global economic recession and its grave impact on health is anticipated to greatly contribute to the establishment and/or promotion of those health infrastructures, policies and services that are necessary to support effectively the control of these disorders.

Thalassaemia and Liver disease
Amongst the vital organs affected as a result of the pathophysiology of the disease itself and/or its treatment (blood transfusion) include the endocrine, heart and liver. Iron related heart complications constituted for years (and still do in many countries) the first cause of morbidity and mortality amongst mainly patients with β-thalassaemia major (transfusion dependent) globally. Scientific and research focus, however, in the last two to three decades, mainly in the EU and North America on reducing such complications, have indeed led to the development of
mainly MRI-based technologies (e.g. T2*, R2) for accurately assessing and monitoring heart iron load and heart function\(^6\). These, coupled with the significant improvements in iron chelation and promotion of personalised, tailored to individual needs care, have led to significant reductions in the number of patients with heart complications and death rates\(^6\).

But then again, such tools and protocols have not been adopted by many countries (from where approved treatment is accessible and free) and todate lack of accurate and specific measurement of iron in heart and inappropriate or lack of assessment of heart function remain serious concerns for still large patient populations across the world and important challenges for TIF.

In this particular report TIF is bringing to the forefront liver disease – a medical consequence of both iron load and viral infection mainly caused by transfusion related hepatitis viruses\(^10\). Liver disease is another yet important cause of morbidity and mortality amongst these patients, worldwide, today emerging as the first cause in those countries which have managed to achieve significant reduction of cardiac related morbidity and death as mentioned above.

Chronic liver disease associated with viral infections mainly of Hepatitis viruses (B and/or C) and/or iron deposition in liver, plays an important role in the prognosis of thalassaemia major. Worldwide from 4 % to more than 85% are positive for antibodies to HCV (see table below)\(^11\)\(^12\).

<table>
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<th>Reference</th>
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<th>Anti-HCV(^+), %</th>
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ND indicates not done.

In the third countries, ME, ASIA and West Pacific, the prevalence of HBV and HCV chronic infections are higher and in the absence or presence of suboptimal national blood safety measures, such infections are still occurring and in some of these countries at high rates. In the industrialised world: (i) since the discovery of the HCV, (ii) the development of extremely sensitive and specific testing of HCV and HBV [including Nucleic Acid Testing – (NAT)], (iii) the implementation of HBV vaccination programmes and (iv) the promotion of non-remunerated
voluntary blood practices, the residual risk of transmission of these pathogens through blood and its products has been dramatically reduced to extremely low levels, as low as 25 per 1 million donations in USA, Canada and several European countries\textsuperscript{13}. Today, in these countries, almost exclusively older patients with transfusion depended \(\beta\)-thalassaemia who have received transfusions before the 1990s are HBV and/or HCV infected. Transmission of these infections today in such countries is limited to blood units collected mainly during the ‘Window period’ i.e. the period between the time of infections and the time when antigens or antibodies of the viruse (B or C) become detectable in the serum. And although zero transmission may never be achieved, this window period is closing down significantly where DNA-based testing (NAT) is applied. Further to transfusion related liver infections iron deposition in the liver constitutes another major contribution to liver disease\textsuperscript{14} both on its own and possibly through causing aggravation of existing/established HCV and/or HBV infections. Accurate and regular assessment of liver iron content is thus essential to tailor effectively iron chelation therapy to achieve negative iron balance.

The early and specific diagnosis of HBV and/or HCV related chronic hepatitis, regular monitoring of appropriate serological markers and clinical evaluation and importantly the identification of patients at risk of developing liver complications and who may obtain a benefit by antiviral treatment are of pivotal importance and constitute essential components of the multidisciplinary care of these patients.

Liver disease related to iron load is also an emerging challenge in Non Transfusion Dependent Thalassaemias (NTDTs) where the pathophysiology and iron metabolism and accumulation differ significantly from those described for transfusion dependent \(\beta\)-thalassaemia major\textsuperscript{15}. This report however, will focus only on Transfusion Dependent Thalassaemias (TDTs) which carry the additional burden of HCV/HBV infections acquired mainly through transfusions and are in need of antiviral treatment. More specifically this position paper will review the current needs with regards to Chronic HCV infection.

The main issues in the evaluation of chronic liver disease in TDTs infected with HCV and/or HBV are related to the need of specific and regular assessment of liver inflammation, fibrosis/cirrhosis, measurement of iron overload and HCV and/or HBV and liver serological markers.

**TDT, liver disease and Chronic Hepatitis C(CHC)**

The problem of cirrhosis in such patients ranges from 10% to 20\%\textsuperscript{16}. Male sex, high serum, ALT values, positive HCV-RNA and high liver iron content are all significantly associated with severe fibrosis or cirrhosis\textsuperscript{17}. Cirrhosis being a risk factor for the development of Hepatocellular Carcinoma (HCC) and a major cause of liver failure, makes this group of patients a highly vulnerable group for adverse progression to serious liver disease.

**Therapeutic and monitoring Options**

It is thus essential to treat HCV infected patients with TD thalassemia.

As anticipated, the main goals of antiviral treatment are the eradication of the viruse, the control of liver inflammation and the prevention of cirrhosis. Today, the gold standard of care for the treatment of all individuals with CHC with or without compensated cirrhosis is the combination of a pegylated interferon and ribavirin (48 weeks) to patients with genotype 1+4 and 24 weeks to those infected by genotype 2 or 3\textsuperscript{18}. International guidelines recommend termination of treatment after 12 weeks in those patients with genotype 1 or 4 whose serum HCV-RNA levels have not decreased by at least 2 log units compared to the baseline.
Responses in thalassaemia

Unfortunately and despite the magnitude of the problem in TD thalassaemia, the number of patients infected with HCV that receive antiviral treatment for CHC (and/or CHB) is globally very small (the majority in Europe) to draw definite conclusions on any differences between the rates of sustainable viral responses (SVR) obtained amongst thalassaemia patients and those obtained in the general population (without thalassaemia).

Patients with thalassaemia infected with different genotypes of HCV have shown variable SVR rates to different types of antiviral therapy available at times: (a) with α-recombinant interferon monotherapy 28%-80%, (b) with α-recombinant interferon and ribavirin 45% - 100%, (c) with pegylated interferon alone 33% - 46% and (d) with pegylated interferon and ribavirin 25%-64%11.

The common concern in all treatment protocols involving ribavirin published todate albeit the small number involved, is the increase in blood transfusion requirements by between 30% - 60% due to ribavirin associated haemolysis in a percentage of patients which may vary in levels from low to significant with consequent needs of strengthening of chelation requirements19.

The existing data even if not large, suggest that antiviral treatment is essential to be provided where criteria are fulfilled, to prevent progression to serious liver disease. Combination treatment with Peg-interferon and ribavirin has demonstrated satisfactory SVR rates including in Genotype 1 cases and should thus currently be recommended in these patients35. The increased blood requirements to maintain Hb to recommended levels of more than 9g/dl (TIF Guidelines) may be acceptable and well managed in multiply transfused patients both in those with a high probability of obtaining SVR i.e. genotype 2 or 3, absence of cirrhosis and low liver iron concentration (as measured by a validated method prior to treatment) but also in those with poorer prognosis for SVR e.g. Genotype 2 or 3 with cirrhosis or genotype 1 with or without cirrhosis.

However, despite improvements in treatments of HCV infection, almost 50% of HCV infected patients (with or without thalassaemia) cannot be cured with this standard combination therapy. There is therefore, an urgent need to treat those patients that either have failed previous cycles (either partial or relapses) or have not responded at all to the above standard combined antiviral treatment and in particular those with the poorer prognosis.

These patients with the exception of those with regular and accurate liver iron measurements, need to be monitored regularly and appropriately (as clearly recommended by EASL – AASL) in order to identify those that can be offered treatment with new drugs that have recently become available. Already two new antiviral drugs, telaprevir and boceprevir (HCV NS3-prolease inhibitors) have recently received marketing authorisation in 2011 from FDA and EMA to be used in combination with the existing standard combination treatment. This is considered as an intensified antiviral treatment and is mainly recommended for relapses of genotype 1 (although it is also licensed as a first line drug that may be used for naïve patients with anticipated poor prognosis to standard care). Other compounds/drugs are also in various phases of development such as: (i) other NS3 protease inhibitors, TMC435, B1201335 (in Phase III), others in Phase II, Phase I and preclinical, (ii) inhibitors of HCV replication (NSSA, NSSB) in Phases II, I and preclinical and (iii) host targeting agents including immunomodulatory agents such as Interferon λ (in Phase II) and GS-9620 (in Phase I)11.

Some of the future goals being to create antiviral combinations limiting the emergence of drug resistance and the avoidance or exclusion of the use of Interferon altogether11.

Safety profile and monitoring TD thalassaemia during combined treatment.
Antiviral treatment in thalassaemia needs close monitoring in patients with cardiovascular diseases while not indicated in those with decompensated myocardopathy or severe disorders of cardiac rhythm at the end.

Continuous haematological monitoring to detect anaemia is essential to allow prompt and accurate adjustment of transfusion therapy and subsequently of iron chelation. In addition close monitoring of development of neutropenia is essential. It may be necessary to switch iron chelation drugs during antiviral treatment to prevent additional risk of chelators or other drugs known or expected to be related to neutropenia further to that known to be related to the use of Interferon.

Today further to the standard laboratory and clinical testing and monitoring (as described in official recommendations of EASL/AASL) new tools are emerging that may prove to contribute significantly to: (i) the prediction of responses to antiviral treatment and to (ii) the prediction of progression to severe liver disease. ‘Favourable genotypes’ or polymorphism identified through genome wide association studies of the IL 28B gene coding for the Interferon are associated with the control of HCV infection in TM patients in terms of spontaneous clearance, progression of liver fibrosis and response to Interferon.

Identification of this polymorphism is demonstrated to be associated with an increase of approximately two fold incidence of SVR in HCV genotype 1b CH patients treated with Pegylated Interferon + Ribavirin.

Side Effects
The profile of contraindications, side effects and adverse events related to the use of each authorised antiviral drug is well described in each one’s package leaflet information but also widely published in literature. In thalassaemia specifically, the major concern has always been the Ribavirin related anaemia as discussed previously. Certainly in a chronic multi-organ disease such as thalassaemia, other side-effects such as weight loss and psychosocial issues are equally concerning and may in fact constitute serious reasons for patients to terminate treatment.

In the case of the two new drugs each provided in the context of triple therapy with Pegylated + Ribavirin, anaemia (additional to that related to Ribavarin) constitutes a major side toxicity. With an Hb reduction of 3 g/dl or more seen (not in patients with thalassaemia but in the general population) in 55% of the patients taking teleprevir for example (vs 25% of cohort patients) certainly warrants new concerns.

However, the drugs’ associated haemolysis in patients with β-thalassaemia major, who are receiving regular transfusion therapy, as mentioned previously, does not appear to be of a major challenge since appropriate and calculated increase in RBC transfusions with concomitant tailoring to the individual patient intensification of iron chelation therapy may well counter balance this negative effect.

Recommendations
Although tailored based anti-viral treatment may be necessary and due to the different medical complications of each patient with thalassaemia, some recommendations for treatment of thalassaemia patients with chronic HCV hepatitis include.

- Combination therapy with Peg-interferon plus ribavirin should be suggested to patients with HCV chronic hepatitis or compensated cirrhosis (moderate quality of evidence in thalassemia patients).
• The therapy should be administered for 48 weeks to patients infected by genotype 1 or 4, and for 24 weeks to patients infected by genotype 2 or 3 (moderate quality of evidence in thalassaemia patients).

• In patients infected with genotype 1 or 4, antiviral therapy should be withdrawn after 12 weeks if serum HCV-RNA levels have not decreased by at least 2 log units compared with baseline (moderate quality of evidence in thalassaemia patients).

• An increase in the number of blood transfusions during the antiviral therapy may be required to maintain haemoglobin level more than 9g/mL (moderate quality of evidence in thalassaemia patients).

• Intensification of chelation treatment before starting antiviral treatment should be considered in patients with severe iron burden (low quality of evidence in thalassaemia patients).

• Clinical monitoring of liver disease is necessary in thalassaemia patients with HCV chronic hepatitis or cirrhosis who have contraindications to antiviral therapy or have failed previous antiviral therapy.

It is thus of utmost importance for all patients with β-thalassaemia major, irrespective of HCV genotype, iron load, presence or absence of cirrhosis, who are infected with HCV to receive treatment as reported through EASL recommendations¹¹ and by others¹⁸.

And although inclusion of these patients in the context of the currently provided triple treatment using one of the two new drugs (as mentioned above) to the standard/combined therapy, serious consideration by medical specialists to treat those patients with thalassaemia that have not responded to standard combined treatment mainly of Genotype 1 may be essential to prevent progression to serious liver disease such as HCC.

It is unfortunate that to date and despite the reference to the haemoglobinopathies in the EASL recommendations for antiviral treatment of HCV infection, provision of such treatment to patients with thalassaemia is very limited mainly because of the contraindications described in the package/leaflet information of Ribavirin (and because of costs in many third countries).

There is an urgent need for our global patient community to initiate a process of discussion with medical experts in the field, the industry and regulatory authorities requesting the revision of the context of the package leaflet of Ribavirin. This will allow the medical community to provide with more confidence antiviral treatment to all those patients that are in need and the national health authorities to consider and amend their reimbursement policies for this treatment. It addition, it is of pivotal importance to join hands with European and international groups of patients infected with HCV to encourage and motivate for more research and focus on new medicines as well as on patients’ education. For the thalassaemia patient communities in particular it is extremely important to pool knowledge and experience around the various treatment protocols and drugs used, responses and side effects reported through the years.

**Conclusion**

Patients with thalassaemia even when given optimal iron chelation develop iron-induced liver damage. Certainly the more personalised medical care including iron chelation tailored to the individual’s needs may minimise iron deposition in countries where such protocols are
encouraged and implemented. Furthermore, iron load and HCV infection have been shown to be two different independent risk factors for progression of liver fibrosis. Unfortunately until now patients with Hb disorders have been traditionally excluded from large studies of therapy of HCV, particularly where ribavirin was involved including the most recent trials with the two new drugs.

Treatment of HCV infection has been shown to decrease the liver inflammation in thalassaemia to similar levels as in HCV infected population without thalassaemia. Side effects or adverse consequences related to the use of ribavirin have been shown in a number of studies to be well managed.

Considering the extent of HCV infection in this patient population globally, it is of pivotal importance for the medical community to urgently revise the existing practices and promote the provision of antiviral treatment to patients with thalassaemia. It is equally essential to encourage and initiate a dialogue with relevant companies to include patients with haemoglobinopathies into clinical trials with new components currently under or upcoming research studies. At the same time it is of immense value to promote the conduction of safely trials with the two newly already authorised (since 2011) drugs in order to better define the particular and specific consequences, safety and risk profiles of their use in these patients. This may not only involve the haemolysis associated with the use of ribavirin but also others which may be related to the disease pathology and drug/drug interaction considering the large gamma of drugs these patients are taking to address a wide range of medical needs.

TIF proposes to focus in the next three years to promote the above through:

- creating a strong Liver Disease network to review the existing Guidelines and recommendations in view of new technology and information on the better and more appropriate follow up and monitoring of the antiviral treatment of patients with thalassaemia major infected with HCV and propose a new section to be included in TIF’s Guidelines to be revised in 2013;
- working closely with EASL/AASL to include a special section of recommendations of patients with haemolytic anaemias including thalassaemia in collaboration and with the active participation and involvement of patients e.g. TIF;
- proposing changes/amendments to regulatory authorities (EMA, FDA) in relation to the contraindication context of Ribavirin in haemolytic anaemias as described in the information package leaflet of the drug;
- establishing an official line of communication with relevant industries/product manufactures with the aim: (i) to promote the conduction of safety trials both with the existing standard combined treatment and with the two new drugs and (ii) to promote the inclusion of patients with Hb diseases in large clinical trials with the new drugs that are under or upcoming clinical trials;
- supporting the establishment of close collaboration with: (i) European patient associations in the field of thalassaemia and liver diseases e.g. European Liver Patients Association (ELPA), (ii) European and American medical professional associations (EASL, AALS), (iii) World Hepatitis Alliance and World Health Organisation, and (iv) other disease oriented associations focused on the promotion of quality care for patients in Europe e.g. Eurordis and internationally such as IAPO ;
- encouraging National Health Authorities (NHA) through this position paper in every country to support and promote at least the standard combined antiviral treatment of patients with thalassaemia infected with CHC and/or CHB;
- supporting member associations to continue and strengthen their advocacy campaign (i) on the safety of blood (ii) voluntary non remunerated blood donation practices, (iii) the adoption
and implementation of the EU and other Directives and regulations on Blood Safety and the appropriate laboratory technologies such as NAT and pathogen inactivation (hopefully coming soon for RBC) and (iv) the regular specific laboratory testing and clinical monitoring of liver iron load, liver disease and HCV infection. Strong laboratory and imaging infrastructures are necessary to be in place in order to make accurate assessment prior, during and post treatment to enable medical specialists to make the right decisions, when to initiate, when to stop, when to continue and when to change or strengthen the antiviral treatment for safe and effective outcomes. This infrastructure includes assessment of Liver Iron Content (LIC), fibrotest, fibroscan, ultrasound, liver biopsy (where essential) and others according to EU and international guidelines of monitoring patients with CHC.
References


18. EASL Journal of Hepatology 2011 vol 55/245-264


