# Treatment of hepatitis C in patients with thalassemia

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The combination of chronic transfusion and iron chelation therapies has dramatically changed life expectancy and quality of life for patients with thalassemia major.[1] The development of oral chelators has reduced overall and cardiac mortality[2] and further improvements of chelation effectiveness are likely through better compliance and extended 24 hours/day chelation coverage.[3,4] Hemopoietic stem cell transplantation is a widely performed procedure which offers the possibility of definitively curing thalassemia.[5] However, with the dramatically improved survival of patients with thalassemia major, care providers face new clinical scenarios and new challenges associated with the longer life and aging of these patients.

Liver disease has long been recognized as an important cause of morbidity and mortality in patients with thalassemia.[6] The relevance of liver disease has been further underlined by the recent report of cases of liver cancer in adult patients with thalassemia.[7]

## Epidemiology of hepatitis C virus infection

Hepatitis C virus (HCV) infection is a major, worldwide health problem: it is estimated that more than one hundred million people are infected.[8] While rigorous donor screening and testing procedures have dramatically reduced transmission of HCV via blood products, there are still many countries in which standards of blood product management do not adequately protect chronically-transfused patients from this complication.

## Epidemiology of hepatitis C virus infection in patients with thalassemia

Among thalassemic patients transfused before the 1990s, the prevalence of HCV infection was shown to be proportional to the number of units of blood received, and approached 80% in the adult patients.[9,10] In countries with a high Human Development Index, the rate of new infection in thalassemia patients has dropped markedly in recent years but this has not been the case in countries with a low-medium Human Development Index. This was demonstrated by unpublished data from a survey conducted by Androulla Eleftheriou on behalf of the Thalassaemia International Federation (TIF) which covered the period from 2005 to 2007 (Figure 1). With the large majority of chronically-transfused patients living in underdeveloped or developing countries, HCV infection remains a significant problem for patients with thalassemia major.

## The clinical/biological challenge of hepatitis C virus infection in patients with thalassemia

The severity of HCV-related liver disease is strongly influenced by the presence of co-existing factors and morbidities. Both iron overload and HCV infection lead, albeit through different mechanisms, to hepatocellular necrosis, fibrosis and cirrhosis. Figure 2a and 2b show a case of active HCV-related hepatitis in an iron-overloaded liver of a patient with thalassemia: iron granules, lymphocyte infiltration and fibrosis are evident. A prospective study on thalassemia patients who survived hemopoietic stem cell transplantation demonstrated, through repeated liver biopsies, that HCV infection and iron overload are independent but mutually reinforcing risk factors for the progression of fibrosis and development of cirrhosis. The 10-year probability of progression of fibrosis reached 80% in patients with severe iron overload and HCV infection,[11] whereas in patients with good control of iron overload, the rate of such progression appeared insignificant in HCV-negative patients and limited to approximately 20% in HCV-positive patients in the same period of observation (Figure 3). In this issue of the journal Di Marco *et al.* demonstrate that good control of iron overload and treatment of HCV infection can limit progression of fibrosis in thalassemia patients receiving medical therapy.[12] A clear message emerges from these and other studies: with proper control of iron overload, based on accepted clinical, diagnostic and therapeutic guidelines,[4] and proper prevention or therapy of HCV infection, progression to fibrosis and development of cirrhosis can be either prevented or greatly delayed.

## Therapy of hepatitis C virus infection in the non-thalassemic population

The medical treatment of HCV infection in the non-thalassemic population has undergone remarkable improvements in the last few years. The initial successes of trials with recombinant interferon were magnified by the introduction of ribavirin, pegylated interferon and finally the association of the two drugs (Figure 4). Several practice guidelines are now available with well-defined evidence-based recommendations[13] regarding the choice of specific drugs, timing of treatment, therapeutic associations and side effects. The best outcome has been obtained with the association of pegylated interferon and ribavirin for a period of time which depends on the viral genotype, ranging from 24 months for genotypes 2-3 to 48 months for genotypes 1. In addition, there is reasonable consensus on how long treatment should be continued before it is considered to have failed.[13]

Ribavirin is a nucleoside analog with a broad spectrum of antiviral activity which appears to decrease hepatitis C virus infectivity in a dose-dependent manner;[14] its mode of action is not completely understood. Ribavirin is generally well tolerated, but a major

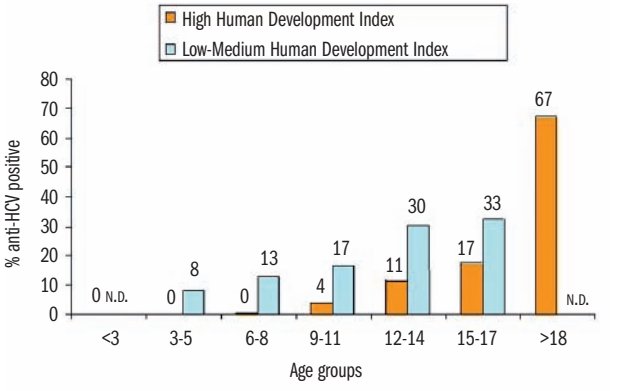


**Figure 1.** Incidence of anti-HCV positivity in thalassemic patients in different age groups in countries with a high Human Development Index and in those with a medium-low Human Development Index (data not available for patients less than 3 years and over 18 years old in countries with a low-medium Human Development Index). Unpublished data from a survey conducted in years 2005-2207 by the Thalassaemia International Federation. Courtesy of Androulla Eleftheriou.

adverse effect is hemolysis[15] related to oxidant damage.[16] Anemia requiring dose reduction occurs in 15% of patients; this adverse effect is particularly severe if anemia is already present. Hemolysis is reversible after discontinuation of the drug. In addition, chronic hemolysis induced by prolonged therapy with ribavirin can lead to increased deposition of iron in the liver although this is negligible in the normal population.[17] Despite this potentially severe complication of ribavirin therapy, the association of pegylated-interferon plus ribavirin remains the best available treatment for HCV infection in non-thalassemic patients.

### *Therapy of hepatitis C virus infection in patients with thalassemia*

The hemolytic effects of ribavirin assume much greater significance in patients with thalassemia. Initial limited trials with interferon plus ribavirin in patients with thalassemia resulted in a 30% increase of blood requirement[18] and prompted an associated increase of chelation therapy.[19] This led to specific contraindication to the use of ribavirin in thalassemia and other hemolytic anemias (Copegus® prescribing information).

In this issue of the journal, Harmatz *et al.*[20] present a report on the safety and efficacy of the association of pegylated α-2 interferon and ribavirin in patients with thalassemia. Despite a limited study cohort (21 patients of whom only 16 completed the treatment plan), the report clearly confirms the therapeutic efficacy of this association and shows that the expected increase in blood requirement is manageable. Moreover, while transfusion requirements increased, as expected, by 44% only four patients (29%) showed an increase of hepatic iron concentration > 5 mg/g dry weight and overall liver iron remained stable. No patient developed iron-related cardiac, liver or endocrine toxicity although neutropenia was a frequent side effect. The chelation efficiency of deferox-

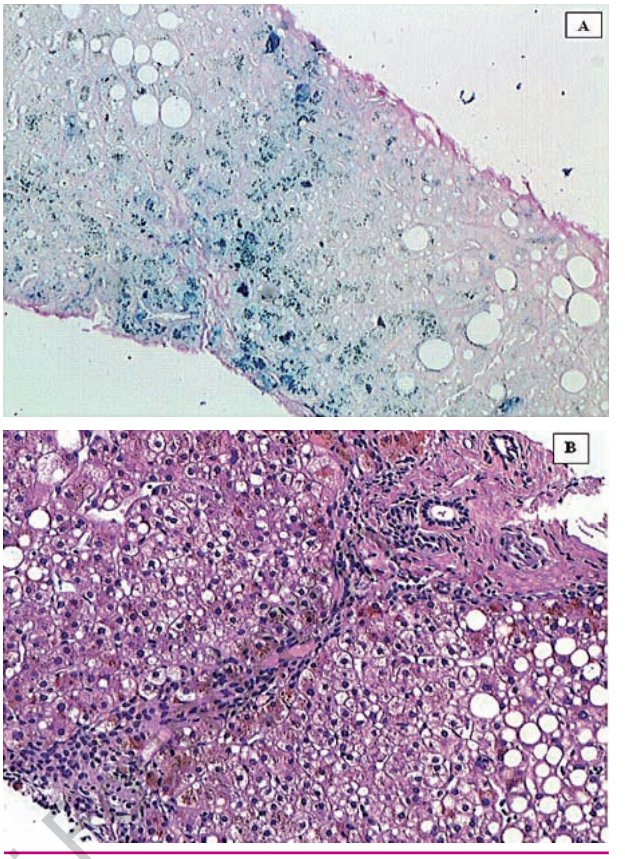


**Figure 2.** Liver biopsy slides from an HCV-positive thalassemia patient. (A) (Perls' stain x 200) Iron deposits in hepatocytes and Küpffer cells. (B) (Hematoxylin and eosin stain, x 200) Columns of hepatocytes crossed by a port-portal bridge. Bile canaliculus regeneration. Lymphocyte infiltration characteristic of active hepatitis. Severe deposition of iron granules in hepatocytes and Kupffer cells. Small and medium steatotic vacuoles. (Courtesy of Marco Rais, MD).

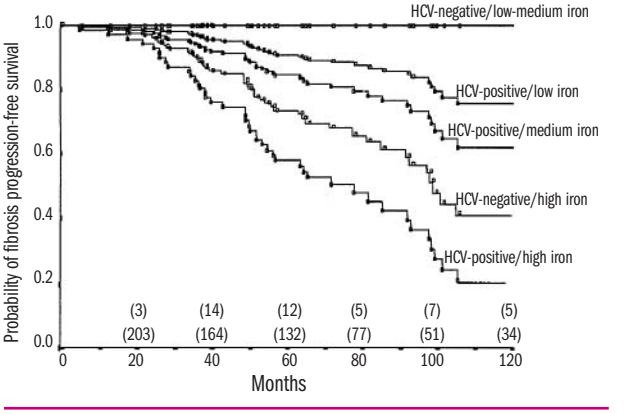


**Figure 3.** Probability of fibrosis progression-free survival by iron and HCV status. Patients were stratified into six groups according to hepatic iron concentration and HCV status. HCV-negative patients with low or medium concentration of hepatic iron did not show progression of fibrosis and were grouped together. There were 62 HCV-negative patients with low-medium iron (0.5-12.7 mg/g dw); 32 HCV-positive patients with low iron (0.5-5.6 mg/g dw); 43 HCV-positive patients with medium iron (5.7-12.7 mg/g dw); 27 HCV-negative patients with high iron (12.8-40.6 mg/g dw); and 37 HCV-positive patients with high iron (12.8-40.6 mg/g dw). *This research was originally published in Blood: Angelucci E. et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002;100:17-21. ©the American Society of Hematology.*

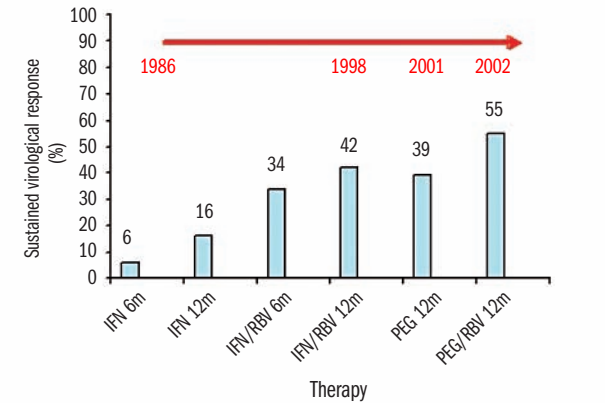


**Figure 4.** Improvement of sustained virological response induced by anti-HCV therapy over the years in the general, non-thalassemic population. (IFN, interferon; RBV, ribavirin; PEG, pegylated interferon; m = months).

amine seems to improve with a reduction of liver inflammation.

The study by Harmatz *et al.*[20] makes a significant contribution to the debate on the optimal therapy of HCV infection in the setting of thalassemia. A cost/benefit ratio analysis clearly shows the significant advantage of using the best available therapy (pegylated interferon + ribavirin) even in the setting of this special patient population. Since a large number of thalassemic patients can now live well into their forties, it seems unwise to deny them the best available indicated treatment for this important and potentially long-term fatal complication. Development of new chelators, greater understanding of chelation therapy and better methodology to determine and quantify iron overload[4] clearly enable more intense transfusion and chelation therapy to be managed for a limited period of time. Providing that treatment is conducted in centers able to adequately manage chelation and antiviral therapy, the association of pegylated interferon and ribavirin should be considered for the treatment of HCV infection in all patients with thalassemia.



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