

Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel

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Chelation therapy with new drugs prevents cardiac damage and improves the survival of thalassemia patients. Liver diseases have emerged as a critical clinical issue. Chronic liver diseases play an important role in the prognosis of thalassemia patients because of the high frequency of viral infections and important role of the liver in regulating iron metabolism. Accurate assessment of liver iron overload is required to tailor iron chela-

tion therapy. The diagnosis of hepatitis B virus- or hepatitis C virus-related chronic hepatitis is required to detect patients who have a high risk of developing liver complications and who may benefit by antiviral therapy. Moreover, clinical management of chronic liver disease in thalassemia patients is a team management issue requiring a multidisciplinary approach. The purposes of this paper are to summarize the knowl-

edge on the epidemiology and the risks of transmission of viral infections, to analyze invasive and noninvasive methods for the diagnosis of chronic liver disease, to report the knowledge on clinical course of chronic viral hepatitis, and to suggest the management of antiviral therapy in thalassemia patients with chronic hepatitis B or C virus or cirrhosis. (*Blood*. 2010;116(16):2875-2883)

Introduction

In the last 4 decades, regular blood transfusions and chelation therapy have improved the survival of patients with thalassemia major.¹⁻³ Despite the progress on chelation therapy, cardiac complications remain the main cause of death among transfusion-dependent thalassemia patients related to the susceptibility of cardiac cells to iron overload toxicity.^{4,5} The interest in the clinical management of chronic liver diseases has been increasing, however, because of the high prevalence of viral infections in adult transfusion-dependent thalassemia patients and the central role of the liver in regulating the iron metabolism.^{5,6}

The assessment of heart and liver iron overload is required to tailor iron chelation therapy. Furthermore, the diagnosis of hepatitis B virus (HBV)- or hepatitis C virus (HCV)-related chronic hepatitis is required to identify patients who have a high risk of developing liver complications and who may obtain a benefit by antiviral therapy.

The goals of this paper are to summarize the epidemiology and the risks of transmission of viral infections, to analyze invasive and noninvasive methods for the diagnosis of chronic liver disease, to report the knowledge on clinical course of chronic viral hepatitis, and to suggest the management of antiviral therapy.

Methods

The panel of experts identified 5 main questions: (1) What proportion of thalassemia patients has chronic viral infections? (2) What are the risks of acquiring viral infections and what are the risks of transmission? (3) What are the currently available tests and methods for diagnosing viral infections and managing chronic liver disease? (4) What is the risk of developing cirrhosis, hepatocellular carcinoma (HCC), and death of liver failure in thalassemia patients with chronic viral hepatitis? (5) What are the therapeutic options for thalassemia patients with HBV and/or HCV chronic hepatitis?

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Table 1. Grading of Recommendations Assessment Development and Evaluation (GRADE) system: quality of evidence and definitions

Quality level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Data are from Guyatt et al.¹²

An expert hepatologist prepared an initial draft based on systematic review of published literature by Medline search on viral hepatitis in thalassemia patients, examined recently published guidelines on the diagnosis, management, and treatment of chronic hepatitis B and chronic hepatitis C edited by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian-Pacific Association for the Study of the Liver⁷⁻¹⁰ and the Consensus Development Conference sponsored by the National Institutes of Health.¹¹ Recommendations of the panel of experts were based insofar as possible on evidence from publications that reported data on thalassemia patients. If evidence from thalassemia patients was unavailable, the panel selected recommendations from published guidelines that were suitable for thalassemia patients. Recommendations were evaluated according to the Grading of Recommendations Assessment Development and Evaluation system and classified into 3 levels: high, moderate, or low¹² (Table 1). For each recommendation, the level of evidence (high, moderate, or low) and population studied (general population of patients with viral chronic hepatitis or thalassemia patients) was specified. The panel of experts discussed the draft issue by issue, and 3 experts on blood transfusion, iron metabolism, and viral hepatitis management reviewed the recommendations. Finally, 8 international external experts in pediatrics, hematology, and viral hepatitis reviewed and criticized the recommendations.

Results

What proportion of thalassemia patients have chronic viral infections?

Worldwide, from 0.3% to 5.7% of thalassemia patients are hepatitis B surface antigen (HBsAg)-positive¹³⁻²⁰ and from 4.4% to 85.4% are positive for anti-hepatitis C antibodies¹³⁻²⁷ (Table 2). The prevalence of HBV chronic infection is higher in Asia and Southeast Asia countries, whereas HCV chronic infection is widespread throughout the world. Among HCV-infected thalassemia patients, the most common genotype is the genotype 1b^{16,21,28-35} (Table 3). Other hepatotropic viruses, such as GB virus C and transfusion transmitted (TT) virus, are also common among thalassemia patients but have not been found to contribute to chronic hepatocellular damage.^{36,37}

What are the risks of acquiring viral infections and what are the risks of transmission?

HCV transmission can occur through blood transfusion. The incidence of chronic hepatitis C was higher among thalassemia patients transfused before 1992, when screening of blood donors was still not available. Nowadays transmission of HBV and HCV by transfusion is rare because of mandatory screening of blood products. HBV transmission by mother to infant, sexual contact, or household contact is still common in the intermediate or high

Table 2. Prevalence of HBsAg-positive and anti-HCV-positive thalassemia patients

Reference	Geographic area	Screened subjects, no.	HBsAg+, %	Anti-HCV+, %
13	Iran	732	1.5	19.3
14	Turkey	399	0.8	4.4
15	Thailand	104	2	21.2
16	Lebanon	395	0.3	14
17	India	104	3.8	21
18	Malaysia	85	2.4	22.4
19	Malaysia	72	1	13
20	India	70	5.7	ND
21	Iraq	559	ND	67.3
22	Pakistan	35	ND	60
23	Italy	1481	ND	85.2
24	Bahrain	242	ND	20.5
25	Brazil	32	ND	46.8
26	Hong Kong	99	ND	34
27	UK	73	ND	23.3

ND indicates not done.

endemic area. Finally, the intravenous drug use with contaminated needles is another common cause of both HBV and HCV infection.

Risk of contracting viral infection. Blood transfusions are safe in developed countries. Since the introduction of blood donor screening for HBV and HCV infection, the residual risk has essentially been limited to blood units collected during the “window period,” the period between the time of infection and the time when antibodies against the virus C are detectable in the serum. To minimize even this residual risk, some national health organizations have added determination of HBV-DNA and HCV-RNA by nucleic acid technology to the battery of screening tests. The test is performed on plasma mini-pools of different blood donors.³⁸ The current risk of transfusion-transmitted viral infection is estimated to be less than 2.5 per 1 million donations in the United States, Canada, and several European countries.³⁹⁻⁴¹ The situation differs in developing countries that have not yet incorporated the key requirements for a modern blood transfusion system. Most of these countries are in Asia and Africa.⁴² Vaccination against HBV infection is a key intervention in preventing the transmission of HBV and is a critical strategy in reducing the global morbidity and mortality. Persons immunized against HBV enjoy long-term protection, and countries that have implemented universal hepatitis B immunization have experienced a significant reduction in HBV-related diseases.^{43,44}

Risk of viral transmission to other persons. Both HBV and HCV can be transmitted sexually, but with different efficiency. Sexual partners of HBV carriers are at increased risk of infection and should be vaccinated or should use barrier methods.⁹ Regarding HCV, epidemiologic studies indicate that the risk of sexual transmission is from 0% to 0.6% per year for persons in monogamous relationships.^{45,46} Nonsexual infection of household members (siblings, offspring, and parents) is possible but occurs at low rates. An Italian study examined the risk of HCV intrafamilial transmission and reported that no cases of infection occurred among household contacts (77 parents and 56 siblings) of 44 children with chronic HCV infection (11 with transfusion-dependent thalassemia).⁴⁷ A Greek study found no anti-HCV antibodies in household contacts of 23 HCV-RNA-positive thalassemia patients with chronic hepatitis during a mean observation of 4 years.⁴⁸ Conversely, a cross-sectional study performed in Pakistan found that 20.5% of 341 household contacts of 86 anti-HCV-positive children with

Table 3. Prevalence of HCV genotypes in thalassemic patients with chronic hepatitis C

Reference	Geographic area	No. of subjects	HCV genotypes, %							
			G1	G2	G3	G4	G5	G6	Mixed	
28	Iran	23	50	5	18					27
29	Iran	280	57	1	35					4
30	Italia	139	75.6	16.6	5	3				
31	India	30	26.6		66.6			6.6		
21	Iraq	48	50				35.4			14.6
32	Egypt	78	37.2				62.8			
16	Lebanon	19	37	5	21	37				
33	China	18	77.7						23.3	
34	Australia	27	40	20	40					
35	Greece	28	39	7	35	17				

thalassemia had anti-HCV antibodies.⁴⁹ In another study, performed in India, 16% of 125 first-degree relatives of thalassemia patients with chronic HCV infection were found to be positive for anti-HCV.⁵⁰

The high number of successful pregnancies has provided evidence of the relative safety of pregnancy in women with thalassemia major.⁵¹ In developed countries, the estimated risk of vertical transmission of HCV infection ranges from 2% to 6% and is almost always confined to women who have detectable HCV RNA.⁵²⁻⁵⁴ The mode of delivery does not affect risk of transmission, with similar rates of infection in infants delivered by cesarean section or vaginally.⁵⁵ The role of breastfeeding in HCV transmission has been controversial. However, most authorities agree that breastfeeding carries a very low risk of transmission provided that the nipple is undamaged.^{10,56} Anti-HCV testing in exposed infants is currently recommended at 18 months of age.⁵⁶ If earlier diagnosis is desired, testing for HCV RNA may be performed at 6 months of age.¹⁰

Adherence to standard precautions and vaccination are the most effective means to prevent HBV infection. HBsAg-positive pregnant women should inform their providers so that hepatitis B immune globulin and hepatitis B vaccine can be administered to their newborn immediately after delivery⁴⁴ to help prevent infection in most cases.

Recommendations for counseling and prevention of transmission of HBV and HCV infection

1. All thalassemia patients should receive information regarding the risk of viral infections associated with blood transfusion and other routes, and chronically infected patients with HBV or HCV require counseling on prevention of transmission to other persons (high quality of evidence in the general population and in thalassemia patients).

2. Thalassemia patients who live in countries that have not adopted an immunization program for infants against hepatitis B should strongly consider HBV screening and vaccination before initiating transfusion therapy (high quality of evidence in the general population and in thalassemia patients).

3. Steady-sexual partners of HBV-infected thalassemia patients are at increased risk of infection and should be vaccinated (high quality of evidence in the general population).

4. Infants born to HBsAg-positive mothers should receive hepatitis B immune globulin and hepatitis B vaccine immediately after birth (high quality of evidence in the general population).

5. HCV-positive persons in long-term monogamous relationships should not change their sexual practices (moderate quality of evidence in the general population).

6. Transmission of HCV infection to household members is possible but occurs at low rates (moderate quality of evidence in thalassemia patients).

7. Vertical transmission of HCV infection is possible but is limited to women who have detectable HCV RNA (high quality of evidence in the general population).

8. The existing evidence does not support the choice of planned cesarean section delivery for the prevention of HCV infection (low quality of evidence for general population).

9. Infants born to HCV-positive mothers should be tested for anti-HCV at 18 months of age (moderate quality of evidence for general population).

What are the currently available methods for diagnosis of viral infections and management of chronic liver disease?

Diagnosis of viral infections. Enzyme immunoassay tests to identify HBsAg and HCV antibodies (anti-HCV) are currently used to detect HBV and HCV infection, respectively. A positive qualitative test for HCV RNA, using amplification techniques, such as the polymerase chain reaction (PCR) or transcription-mediated amplification, confirms the presence of viremia in the blood. Quantitative assays measure the quantity of HCV RNA in blood using either target amplification (PCR, transcription-mediated amplification) or signal amplification techniques (branched DNA assay).⁵⁷ A positive qualitative or quantitative HCV RNA test in blood identifies patients with active HCV replication. In contrast, anti-HCV-positive, but HCV-RNA-negative patients have had a previous HCV infection from which they are cured. This is an important issue because the rate of HCV RNA positivity among anti-HCV-positive thalassemia patients is approximately 50% and is lower than in other HCV-infected populations.⁵⁸ The determination of HCV genotypes is very useful to predict the efficacy of antiviral therapy, and quantitation of HCV RNA during treatment can be used to monitor response to therapy.⁵⁷

Quantification of HBV DNA in blood is a crucial component in the evaluation of patients with chronic HBV infection and in the assessment of the efficacy of antiviral treatment. Serum HBV-DNA levels should be expressed universally in international units per milliliter as standardized by the World Health Organization. HBV DNA assays that use real-time PCR technology with improved sensitivity (5-10 IU/mL) and wider dynamic range (up to 8-9 log₁₀ IU/mL) are available. The cut-off point of 2000 IU/mL is generally used to distinguish inactive chronic carriers of HBV from patients with chronic liver disease.^{8,9}

Assessment of chronic liver disease. The main issues in the evaluation of chronic liver disease in thalassemia patients are assessment of liver inflammation and fibrosis and measurement of

iron overload. Until a few years ago, the liver biopsy was the only method available to assess the severity of liver inflammation, the stage of fibrosis, and to measure the liver iron concentration by atomic absorption spectrometry.⁵⁸⁻⁶¹ However, liver biopsy is an invasive procedure associated with some discomfort, and its accuracy for the evaluation of liver fibrosis is questionable in relation to inadequate tissue sampling and intraobserver and interobserver variability.⁶² Finally, severe fibrosis or cirrhosis is responsible for significant variability in iron distribution in thalassemia patients.⁶³

In recent years, noninvasive methods to measure liver iron overload and to assess liver fibrosis in patients with chronic liver disease have been studied. Noninvasive methods for measuring liver iron overload, such as biosusceptometry by superconducting quantum interference device systems and magnetic resonance imaging (MRI), have been evaluated in thalassemia and hemochromatosis patients. After the initial report in 1982,⁶⁴ subsequent studies of superconducting quantum interference device biosusceptometry in clinical applications were limited to only a few specialized centers.⁶⁵

A strong correlation was demonstrated between liver iron concentration by biopsy and by a quantitative measurement of the MRI signal amplitude using the R2 or R2* methodology.⁶⁶⁻⁶⁸ These evidences on accuracy of noninvasive methods for assessment of liver iron concentration are sufficient to consider MRI-R2 methodology as a worldwide available alternative to liver biopsy for liver iron measurement.

Liver biopsy is still considered the “gold standard” for the evaluation of liver damage and is recommended for the assessment of HBV or HCV chronic hepatitis by international guidelines.⁷⁻¹¹ The histologic analysis includes grading of necro-inflammatory damage and staging of liver fibrosis, the evaluation of steatosis, and the diagnosis of cirrhosis, according to standardized scores.^{69,70} In recent years, transient elastography (TE), a technique that uses both ultrasound and low-frequency elastic waves whose propagation velocity is directly related to elasticity of the liver tissue, has been proposed as a noninvasive method for assessment of liver fibrosis.⁷¹ Liver stiffness measurement by TE has been shown to correlate well with the diagnosis of cirrhosis assessed by liver biopsy. This technique has been extensively studied in chronic hepatitis C and appears to be a reasonably accurate method for detection of cirrhosis.^{71,72} A recent study demonstrated that TE is a reliable noninvasive method for diagnosing of cirrhosis in thalassemia patients regardless of the degree of iron overload.⁷³

To date, liver biopsy remains the “gold standard” to evaluate inflammation and fibrosis in thalassemia patients with clinical evidence of liver disease. Alternatively, TE could also be used to define the presence of cirrhosis in centers with expertise on this field.

Recommendations for virologic and clinical evaluation of thalassemia patients with chronic HBV or HCV infection

10. Thalassemia patients who received blood transfusion before 1992 should be tested for anti-HCV antibodies (high quality of evidence in thalassemia patients).

11. HBsAg and anti-HCV tests are recommended in thalassemia patients with elevated serum aminotransferase levels for more than 6 months (high quality of evidence in the general population).

12. Qualitative serum HCV-RNA and quantitative serum HBV-DNA by PCR methods are recommended to confirm the replication of HCV and HBV, respectively (high quality of evidence in thalassemia patients).

13. HCV genotyping should be performed in thalassemia patients with HCV chronic hepatitis before starting antiviral therapy to plan dose and duration of therapy and to estimate the likelihood of response (high quality of evidence in thalassemia patients).

14. MRI using R2 methodology is the recommended noninvasive method for the assessment of liver iron concentration (moderate quality of evidence in thalassemia patients).

15. The liver biopsy is not mandatory before starting antiviral treatment. However, it should be considered to obtain a more accurate assessment of HCV or HBV chronic hepatitis or further information regarding fibrosis stage for prognostic or other therapeutic purposes (moderate quality of evidence in thalassemia patients).

16. Noninvasive methods, such as TE, may be useful in defining the presence or absence of cirrhosis in thalassemia patients with HCV infection (low quality of evidence in thalassemia patients).

What is the risk of cirrhosis, HCC, and death secondary to liver failure in thalassemia patients with chronic hepatitis?

The prevalence of cirrhosis in thalassemia patients ranges from 10% to 20%, as reported in several studies performed in the United States, China, Iran, Italy, and Greece.^{58-61,74,75} Male sex, high serum alanine transaminase values, positive serum HCV-RNA, and high liver iron concentration were all significantly associated with severe fibrosis or cirrhosis.⁵⁸⁻⁶¹

Cirrhosis is a risk factor for the development of HCC and is the major cause of liver failure. A multicenter cross-sectional Italian study reported data from 23 thalassemia patients receiving the diagnosis of HCC during the previous 20 years. The majority of patients had cirrhosis at the time of HCC diagnosis, their median age was 45 years, and 90% of them were anti-HCV positive. Ferritin levels averaged 2000 ng/mL, suggesting a limited role for iron overload in carcinogenesis.⁷⁶ Prevalence was calculated to be approximately 6 times the expected value for the Italian male population, but age-specific comparisons, which would be more appropriate, are not possible because such data are not available. A prospective study identified a 2% incidence in HCC during a one-year period of observation in a cohort of 105 adults with thalassemia major.⁷⁷ In a recent prospective survival analysis, the hazard ratio for death was significantly higher in thalassemia patients with cirrhosis.⁶ In light of these reports, thalassemia patients with HBV or HCV and cirrhosis are at high risk of the development of HCC. The international guidelines suggest that all patients with chronic HBV hepatitis and patients with HCV and cirrhosis should receive liver ultrasound every 6 months for the surveillance of HCC.⁸⁻¹¹

Recommendations for surveillance of HCC in thalassemia patients with chronic HBV or HCV liver disease

17. Thalassemia patients with HBV hepatitis or HCV and cirrhosis have a high risk of developing HCC, and they should receive surveillance with liver ultrasound every 6 months (high quality of evidence in cohort with HCV cirrhosis and low quality of evidence in thalassemia patients).

What are the therapeutic options for thalassemia patients with HBV or HCV chronic hepatitis?

Chronic hepatitis C. The main goals of antiviral treatment are the eradication of virus C, the control of liver inflammation, and the

Table 4. Response to antiviral treatment of chronic hepatitis C

Reference	No. of patients	Status of patients	Treatment	Therapy, mo	SVR, %
80	51	Naive	Interferon- α monotherapy	15	37
78	70	Naive	Interferon- α monotherapy	12	40
81	13	Naive	Interferon- α monotherapy	18	75
34	28	Naive	Interferon- α monotherapy	6	28
83	89	Naive	Interferon- α monotherapy	12	52
84	10	Naive	Interferon- α monotherapy	12	80
87	11	No responders or relapsers	Interferon- α + ribavirin	6	45
86	18	Naive	Interferon- α + ribavirin	12	72
88	3	Naive	Interferon- α + ribavirin	12	100
85	5	Naive	Interferon- α + ribavirin	12	80
90	12	Naive	Peg-Interferon monotherapy	12	33
90	8	Naive	Peg-Interferon + ribavirin	12	63
32	39	Naive	Peg-Interferon monotherapy	12	46
32	39	Naive	Peg-Interferon + ribavirin	12	64
91	4 (genotypes 2, 3)	Naive	Peg-Interferon + ribavirin	6	25
91	12 (genotypes 1-4)	Naive	Peg-Interferon + ribavirin	12	50

prevention of cirrhosis. A sustained virologic response (SVR), defined as the absence of HCV-RNA in serum by a highly sensitive test at the end of treatment and 6 months later, is the marker for efficacy of antiviral therapy. Table 4 shows the efficacy of antiviral therapies of chronic hepatitis C.

Some clinical studies^{34,78-84} showed that α -interferon monotherapy administered for 6 to 15 months induces a sustained biochemical response and SVR in 40% to 50% of thalassemia patients with HCV-related chronic hepatitis. The absence of cirrhosis, low iron hepatic concentration, and infection by HCV genotype other than 1b are the main clinical and virologic findings that predict a good response to therapy. The analysis of data from 139 thalassemic patients treated with α -interferon monotherapy for 48 weeks showed that only 28% of patients infected with genotypes 1 or 4 achieved SVR, whereas 66% of those with genotypes 2 or 3 were cured of viral infection.³⁰ Patients with negative qualitative HCV-RNA test after 12 weeks of treatment had a high probability of achieving SVR; on the contrary, no patients with positive serum HCV-RNA after 12 weeks achieved SVR.⁷⁸

Today, the standard of care for the treatment of chronic hepatitis C and compensated cirrhosis is the combination of a pegylated interferon (Peg-interferon α 2a or Peg-interferon α 2b) and ribavirin. On the basis of the evidence-based data from randomized clinical trials, current treatment guidelines recommend administering this therapy for 48 weeks to patients infected by genotype 1 or 4, and for 24 weeks to patients infected by genotype 2 or 3. International guidelines recommend stopping antiviral therapy after 12 weeks in patients infected with genotype 1 or 4 if serum HCV-RNA levels have not decreased by at least 2 log units compared with baseline on the basis of strong evidence that such patients have a small likelihood of achieving sustained viral response after 48 weeks of treatment.¹⁰

Descriptive studies⁸⁵⁻⁸⁹ have reported data on small cohorts of thalassemia patients treated with α -interferon and ribavirin. The rate of SVR was more than 60%, but blood consumption increased during treatment by 30% to 60% because of ribavirin-associated hemolysis. Indeed, ribavirin, despite being generally well tolerated, induces hemolysis related to oxidative damage. The hemolysis is reversible after discontinuation of the drug, but the increased blood requirement leads to increased iron intake and possible worsening of iron overload. This common adverse event could limit the use of ribavirin in thalassemia, unless great care is taken in monitoring and, if necessary increasing, chelation therapy.

Recently, 3 different studies reported the efficacy and the safety of combination therapy with Peg-interferon and ribavirin in thalassemia patients with chronic hepatitis C. The first reported results of a small randomized study, including 8 patients on monotherapy and 12 patients treated with Peg-interferon and ribavirin.⁹⁰ One-third of the patients treated with Peg-interferon alone obtained SVR versus two-thirds of patients on combination therapy. The second study reported the results of a randomized study, including 78 thalassemia patients with chronic hepatitis C infected with HCV genotype 1 or 4.³² Thirty-nine patients were treated with 1.5 μ g/kg per week of Peg-interferon α -2 monotherapy for 48 weeks, and 39 patients were treated with the same doses of Peg-interferon plus 800 to 1000 mg/day of ribavirin for the same time. SVR was achieved in 46% of patients treated with monotherapy and 64% of patients treated with combination therapy. An increase in blood transfusion and chelation therapy was required in 38% of patients. In the last study, 21 thalassemia adult patients without cirrhosis were treated with Peg-interferon α 2a and ribavirin for 24 (genotypes 2 and 3) or 48 weeks (genotype 1).⁹¹ SVR was achieved by 1 of 4 patients with genotype 2 or 3 and in 6 of 12 patients with genotype 1. An increase in transfusion requirement of 30% to 40% was observed during the treatment. These data suggest that combination treatment with Peg-interferon and ribavirin should currently be recommended in thalassemia patients. Moreover, the increase in the number of blood transfusions required to maintain hemoglobin more than 9 g may be acceptable in patients with a high probability of SVR (genotype 2 or 3 and absence of cirrhosis) and low liver iron concentration measured by MRI before therapy. It must be pointed out that currently used drugs have several adverse events. At the start of treatment, flu-like symptoms, such as fever, chills, and headache, are common. During treatment, depression, insomnia, lack of concentration, hair loss, dry skin, and skin rashes can develop. Severe side effects require immediate withdrawal from treatment. Thalassemia patients with cardiovascular diseases should be closely monitored, and patients with decompensated cardiomyopathy or severe disorders of cardiac rhythm should be excluded from antiviral treatment. Continuous monitoring of hematologic parameters is necessary to detect anemia and neutropenia, which are common adverse events. Because of the high frequency of adverse events related to thalassemia requiring adjustment of transfusion and iron chelation therapy, the management of antiviral treatment in this population must involve a multidisciplinary approach,

including both a hematologist and a hepatologist. Thalassemia patients, on treatment with antiviral combination therapy, require controls of hemoglobin levels every 2 weeks and an adequate supplementation of blood transfusion to maintain hemoglobin levels more than 9 g/L. The use of growth factors for anemia, such as erythropoietin, is not advised. Concerning chelation treatment, whereas deferiprone may increase risk of neutropenia, no findings on the safety of deferasirox in association with combined antiviral treatment have been so far reported in the literature. Therefore, switching to deferoxamine treatment, during antiviral treatment for hepatitis C, should be recommended. In patients with severe neutropenia (absolute neutrophil count < 500/mm³), resulting from interferon treatment, the administration of granulocyte colony-stimulating factor should be advised.

Despite improvements in treatments for HCV infection, almost one-half of patients cannot be cured with standard combination therapy. Patients who have contraindications to antiviral therapy or have failed previous cycles of antiviral therapy should be regularly monitored. This monitoring should include biochemical parameters, ultrasound analysis of liver structure, and TE, if available, every 6 to 12 months to follow the evolution from chronic hepatitis to cirrhosis and to monitor patients with cirrhosis for HCC.

In the near future, 2 new interesting tools regarding the efficacy of antiviral therapy in patients with chronic hepatitis C may be applied to patients with thalassemia. First, recent studies reported that a single nucleotide polymorphism in the IL28B region was associated with an approximately 2-fold higher incidence of SVR in HCV-genotype 1b chronic hepatitis treated with Peg-interferon α and ribavirin.^{92,93} These new findings are associated with other factors, such as age, sex, and viral genotypes, and could be evaluated for thalassemia patients with HCV chronic hepatitis.

Second, direct-acting antiviral agents are in preclinical and clinical stages of development. Results from clinical trials suggest that both protease and polymerase inhibitors increased the rate of SVR when used in combination with Peg-interferon and ribavirin. Although Peg-interferon and ribavirin probably remain a cornerstone of therapeutic regimens in the short-term, combinations of antiviral drugs of different classes, possibly associated with new agents that target host factors or increase antiviral defenses, will create future treatment options.^{94,95}

Recommendations for treatment of thalassemia patients with chronic HCV hepatitis

18. 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).

19. 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 thalassemia patients).

20. 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 thalassemia patients).

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

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

23. Clinical monitoring of liver disease is necessary in thalassemia patients with HCV chronic hepatitis or cirrhosis who have contraindications to antiviral therapy or have failed previous antiviral therapy (moderate quality of evidence in thalassemia patients).

Chronic hepatitis B. Hepatitis B virus infection is a major cause of liver disease for thalassemia patients in developing countries. The clinical course of chronic hepatitis B infection is related to persistence of viral replication. Longitudinal studies indicate that, after diagnosis of chronic hepatitis, the 5-year cumulative incidence of cirrhosis ranges from 8% to 20%. In patients with cirrhosis, the annual incidence of HCC ranges from 2% to 5% and the 5-year cumulative incidence of hepatic failure is approximately 20%.⁹⁶ The indications for antiviral treatment are based on the combination of serum HBV DNA levels, serum aminotransferase levels, and clinical evidence of chronic hepatitis with advancing fibrosis.^{8,9,11} The virologic endpoints to be achieved are different in relation to virologic state (HBeAg-positive or HBeAg-negative) and clinical stage of the liver disease. The analysis of the natural history of HBV chronic hepatitis suggests that the loss of HBsAg may be considered the ideal virologic endpoint because of the decreased risk for development of cirrhosis and HCC, and improved survival. Unfortunately, such seroconversion rarely occurs in response to antiviral therapy. In HBeAg-positive patients, the loss of serum HBeAg followed by appearance of durable anti-HBe seroconversion may be considered a satisfactory virologic endpoint. In HBeAg-positive patients who do not achieve HBe seroconversion and in all HBeAg-negative patients, the suppression of serum HBV DNA levels to as low a level as possible, ideally below the lower limit of detection of real-time PCR assays (10-15 IU/mL), may be considered a desirable endpoint.⁸ Indeed, the suppression of serum HBV DNA levels without emergence of a mutant virus strain has been associated with biochemical remission, histologic improvement, and prevention of complications.⁹⁷⁻⁹⁹

Currently, there are 7 antiviral drugs available for the treatment of chronic hepatitis B: interferon (interferon- α and pegylated interferon), nucleoside analogs (lamivudine, telbivudine, and entecavir), and nucleotide analogs (adefovir and tenofovir). Nucleoside/nucleotide drugs (NUCs) are administered by the oral route and display a powerful inhibitory effect on serum HBV DNA. The choice of drugs should always take into consideration the antiviral efficacy, risk of developing resistance, long-term safety profile, methods of administration, and costs of the therapy.

Two different treatment strategies are applicable in both HBeAg-positive and -negative patients: treatment of finite duration with Peg-interferon or NUCs or long-term treatment with NUCs.

The strategy with a therapy of finite duration is intended to achieve HBeAg loss or HBsAg loss at the end of 48 weeks of treatment. This virologic endpoint is more frequently achieved in HBeAg-positive patients with interferon therapy than with NUCs.⁸ The strategy of long-term treatment with NUCs is necessary for patients who cannot achieve virologic endpoints with a finite therapy and for patients with cirrhosis. Protracted or possibly indefinite therapy with NUCs is necessary in HBeAg-positive patients who do not clear HBeAg and HBeAg-negative patients who achieve a complete serum HBV-DNA suppression. NUCs should be selected according to their antiviral efficacy, risk of developing resistant HBV mutants, safety profile, and cost. The most potent drugs with the optimal resistance profile (tenofovir or entecavir) should be used as first-line monotherapy.^{8,9,11}

Recommendations for treatment of thalassemia patients with chronic HBV hepatitis

24. There are 3 options for the treatment of patients with chronic hepatitis B: treatment of finite duration with Peg-interferon α , treatment of finite duration with NUCs, and long-term treatment with NUCs (moderate quality of evidence in the general population).

25. A finite course of 48 weeks with Peg-interferon α or NUCs indicate in HBeAg-positive patients with the best predictors of HBe seroconversion, including high baseline alanine transaminase values, low serum HBV DNA levels, and genotype A or B (moderate quality of evidence in the general population).

26. Long-term treatment with NUCs is indicated in HBeAg-positive patients who do not achieve an HBe seroconversion with a finite course of Peg-interferon or NUCs and in HBeAg-negative patients. Tenofovir or entecavir should be used as first-line monotherapy because they rapidly reduce serum HBV DNA and have a high barrier to resistance (moderate quality of evidence in the general population).

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Authorship

Contribution: V.D.M., M.C., E.A., C.B.-P., L.P., A.F., M.R.G., P.C., F.G., and F.C. designed research, performed research, identified 5 main questions, prepared an initial draft based on a systematic review of published literature, and discussed the draft issue by issue; A.I. represented the patients who examined the document; D.P., A.P., and A.C. reviewed the document as experts on blood transfusion, iron metabolism, and viral hepatitis management; V.D.M., and A.M. analyzed data and wrote the paper; and P.H., A.K., P.T., D.R., M.D.M., G.F., and J.D.G. criticized the recommendations.

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