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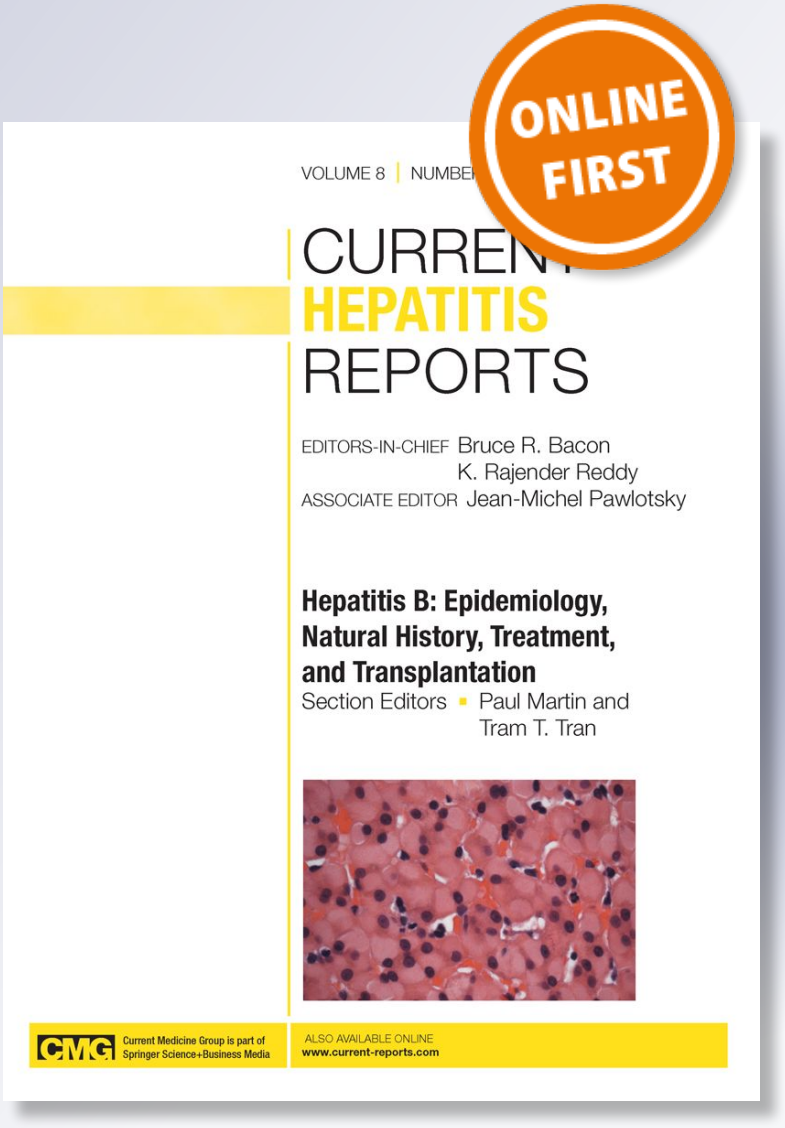

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Treatment of Chronic HCV in Special Populations: Thalassemia, Hemophilia, and Hemodialysis Patients

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Abstract Hepatitis C virus (HCV) infection is a common global health problem. Special patient populations such as those with thalassemia, hemophilia and on hemodialysis are at higher risk for acquiring this infection. Although the incidence of HCV infection has decreased in developed countries, it remains high in developing countries including the Middle East and North Africa region. Management of HCV infection in thalassemia is complicated by severe anemia limiting the use of ribavirin and coexisting iron overload while HCV management in hemophilia patients is more problematic often due to co-infection with HIV. Similarly, chronic kidney disease patients on hemodialysis have special treatment considerations in the management of HCV infection and current guidelines and treatment strategies are largely based on limited data. This review discusses the management the HCV infection in these special populations with emphasis on regional data and considerations.

Keywords Hepatitis C · Hemophilia · Thalassemia · Hemodialysis · Therapy · Epidemiology · Middle East

Introduction

Hepatitis C virus (HCV) is a major worldwide public health problem [1]. It is estimated that over 200 million people are infected and the virus is distributed worldwide with a prevalence varying between different countries from 0.2 % up to 10 % [2, 3•, 4]. Although the prevalence of HCV infection has declined in developed countries because of effective prevention plans [5], it remains high in developing countries [6]. HCV is a leading cause of liver disease, liver failure and hepatocellular carcinoma (HCC), in both industrialized and developing countries [4, 5, 7]. For example, HCV accounts for 20 % of cases of acute hepatitis, 70 % of chronic hepatitis, 40 % of liver cirrhosis, 60 % of hepatocellular carcinomas, and 30 % of liver transplants in Europe [8].

Thalassemia Patients

Hemoglobinopathies are one of the most common genetic disorders with beta thalassemia or thalassemia major affecting mostly developing countries especially in the Mediterranean, Middle East, Far East and East Asia areas [9]. Thalassemia is characterized by decreased or absent globin chains production. The resultant anemia is caused by destruction of the erythroblasts in the bone marrow, peripheral hemolysis of the erythrocytes and ineffective erythropoiesis. The life-long need for transfusions to maintain a hemoglobin level of not more than 9.5 g/dl renders these patients vulnerable to transfusion-transmitted viral infections especially hepatitis C virus [9, 10]. HCV infection is a widespread disease affecting large number of thalassemia patients worldwide and is considered a major public health problem in this high risk group. While rigorous donor screening, testing procedures and suitable donor selection programs have dramatically reduced transmission of HCV via transfusion of blood products, there are still many countries in which standards of blood product management do not adequately protect chronically-transfused patients, especially thalassemia patients, from this complication [7, 11, 12]. Up to 80 % of adult thalassemia patients are infected with HCV in the world [13] but there is tremendous discrepancy

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between epidemiological studies within and between countries in the Eastern Mediterranean region [10]. In a meta-analysis in the Mediterranean and Middle East area, the pooled HCV infection rate was 45 % in Pakistan, 63 % in Saudi Arabia, 18 % in Iran and 69 % in Egypt [10]. Lack of knowledge about blood safety and current HCV seroprevalence is a major threat to public health of these countries. Heterogeneous pattern of geographic distribution of HCV infection in thalassemia patients indicates that the safety of blood before blood screening varies in different countries and may be related to different prevalence of infection and to risk factors in blood donors and the general population [11]. First transfusion before or after the introduction of blood donors screening for anti-HCV antibody is the major determinant of HCV infection in the region. Acute HCV infection is parenterally-acquired and may occur after transfusion of unscreened blood or blood products, intravenous drug use, use of contaminated needles or sharp objects, or rarely from sexual exposure or vertical transmission. Spontaneous clearance of acute HCV occurs with a high rate within the first 12 weeks of infection and depends on the age the person acquires the infection [14, 15]. The younger the age of infection, the higher is the spontaneous clearance rate of HCV. The spontaneous clearance rate of HCV in North American thalassemia patients is 33 % [16]. Because infection with HCV results in chronic infection in a large proportion of infected individuals, it has been suggested that early treatment of acute HCV may abort the development of chronic hepatitis. Several studies have reported on the efficacy of interferon therapy for acute HCV infection in adults. Using interferon α-2b monotherapy for 24 weeks, Jaeckel et al. showed a 98 % sustained virologic response in a cohort of 44 patients with acute HCV infection [17]. The use of the newer pegylated interferons (PEG-IFN) in the treatment of adults with acute HCV was subsequently described with equally excellent results [18]. A single case report showed successful treatment of acute hepatitis C with weight-based dosing of peginterferon α-2b in an 8 year-old child with thalassemia major when high viral load persisted after 12 weeks of the diagnosis of acute icteric HCV infection [19].

Although the natural history of chronic HCV infection in patients with thalassemia is unclear, the morbidity and mortality of those patients is thought to be increased. Liver disease is more severe in HCV-infected patients and may be compounded by hepatic siderosis (Fig. 1). Treatment of HCV in thalassemia patients is aimed at viral eradication, improvement in liver histology, reduction of the risk of hepatocellular carcinoma, and improvement of health-related quality of life and survival. Initial studies using interferon monotherapy have shown a sustained viral response of approximately 30 % [20–22]. Although combination therapy of interferon and ribavirin has replaced monotherapy in HCV-infected individuals, the use of ribavirin in thalassemics has been largely avoided because of

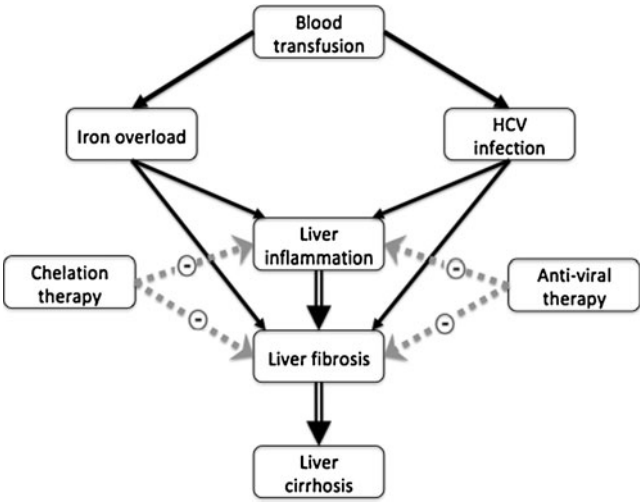

Fig. 1 Interplay of factors in liver injury in transfusion-dependent thalassemia patients with chronic HCV infection

ribavirin-associated hemolysis [23]. Another particular aspect in this patient population is hepatic iron overload which negatively affects the outcome of liver disease [24], often reducing the chance of achieving a sustained viral response with current anti-viral treatments in chronic HCV-infected thalassemia patients [25, 26]. Thalassemia major patients have high iron stores and proper removal of iron with chelating drugs is not successful or may not be properly implemented in all situations. Increased hepatic iron deposition has been shown to correlate with the severity of hepatic inflammation and fibrosis in patients with chronic hepatitis C, and impair response to IFN-based therapy [27, 28]. Some studies have suggested that iron depletion is an adjuvant to antiviral therapy in chronic HCV infection and showed that iron removal and dietary iron restriction could improve the rate of response to IFN [29–31]. Proper management of hepatic siderosis before initiation of HCV therapy in thalassemia patients is therefore essential.

The main limitation in the treatment of HCV infection in thalassemia patients relates to ribavirin use. Consensus statements had listed anemia as an absolute contraindication to ribavirin in hepatitis C, because of the tendency of ribavirin and its metabolites to accumulate within erythrocytes, leading to oxidative damages of red blood cell membranes and hemolysis [32]. Currently, IFN without ribavirin is widely approved as first-line therapy for chronic HCV infection in transfusion-dependent thalassemia patients. Because of hematologic adverse events, ribavirin was however reserved for IFN non-responders or experimental situations [23]. More recently, trials comparing peginterferon monotherapy and the combination of peginterferon and ribavirin have shown considerable increase in SVR rates in the dual therapy arm albeit at the cost of a modest increase in transfusion requirements. In fact, the SVR rates in these

relatively small trials were comparable to treatment-inexperienced patients without thalassemia or hepatic iron overload [33, 34]. Using ribavirin in thalassemia patients increases transfusion need by a median of 30–40 %, but does not increase major adverse events or treatment withdrawal [19, 23]. A summary of the literature on the treatment of HCV in thalassemia is presented in Table 1 [20–22, 33, 35–46]. A meta-analysis showed that thalassemia patients with genotype 1 infection benefit significantly from the addition of ribavirin to their therapeutic regimen with a doubling of SVR rates, from 30 % to 61 %, similar to non-thalassemia patients [23]. Based on the above, we feel the current evidence supports the addition of ribavirin to peginterferon in thalassemia patients with HCV infection. This combination is relatively safe and effective and should be considered particularly in the setting of expert management of hematologic disorders [33, 34].

Hemophilia Patients

Patients with hereditary bleeding disorders were at risk of acquiring HCV infection from factor concentrates in the late 1970s and early 1980s [47]. Virtually all hemophiliacs who were transfused with clotting factor concentrates before 1985 and/or blood transfusions before 1992 were exposed to HCV and approximately 100 % of these are positive for HCV antibodies. The number of new cases has significantly declined because of advances in new technologies for blood products processing and blood screening. HCV prevalence among patients with hemophilia is variable, ranging from 24 % to 95 % in different parts of the world [48, 49•, 50–60]. Hepatitis C is a major reason of morbidity and mortality in infected hemophilia patients and therapy aimed at eradication of the virus aims to improve the quality of life and prolong survival [49•].

Unfortunately, there is not enough or accurate regional data regarding the number of hemophilia patients and the rate of HCV infection in this high-risk group. Most of the Eastern Mediterranean Region Office (EMRO) countries have not reported the number of hemophilia patients with the number varying from 1 patient per 100,000 male in Saudi Arabia and Pakistan to 15.8 patients per 100,000 male in Qatar [61]. In a meta-analysis, the pooled estimate of HCV sero-prevalence in hemophilia patients in the EMRO region was 48.27 % (95 % CI: 36.12–60.43), [62]. The most common HCV genotype in hemophilia-infected patients is 1a followed by 3a [63, 64]. A significant number of hemophilia patients are co-infected with HIV and HCV [65]. Highly active antiretroviral therapy (HAART) has effectively controlled the HIV infection and HCV infection has assumed much greater importance. Indeed, liver disease

Table 1 Summary of the literature on treatment and response of chronic HCV infection in thalassemia patients

Authors	Protocol	IFN doses	RBV dose	Duration (weeks)	Sustained viral	End of treatment	Dropout rate
Clemente et al. [36]	IFN-α2b	3 MU tiw		60	37 %	41 %	0 %
Di Marco et al. [20]	IFN-α2b	5+3 MU tiw		8+18	ND	ND	47 %
Sievert et al. [22]	IFN-α2b	3 MU tiw		24	28 %	28 %	7 %
Spiliopoulou et al. [44]	IFN-α2b	3 MU tiw		72	76 %	100 %	15 %
Artan et al. [35]	IFN-α2a	5 MU tiw		24–48	80 %	ND	0 %
Syriopoulou et al. [45]	IFN-α2a	3 MU tiw		48	52 %	55 %	4 %
Di Marco et al. [37]	IFN-α2b	5+3 MU tiw		8+40	40 %	40 %	4 %
Donohue et al. [21]	IFN-α2b	3 MU tiw		24	ND	ND	0 %
Pizzarelli et al. [43]	IFN-α2a	5+3 MU tiw		24+24	ND	ND	0 %
	IFN-α2b	3 MU tiw				47 %	
Mirmomen et al. [42]	IFN-α2b	3 MU tiw		48	31 %	52 %	7 %
Mirmomen et al. [41]	PEG-IFN-α2a	180 μg/wk		48	43 %	81 %	6 %
Kountouras et al. [39]	PEG-IFN-α2b	1.5 μg/kg/wk		48	13 %	27 %	24 %
Inati et al. [33]	PEG-IFN-α2a+RBV	180 μg/wk	6–10 mg/kg	48	62 %	75 %	0 %
	PEG-IFN-α2a+PLC				33 %	41 %	
Li et al. [40]	IFN-α2b+RBV	3 MU tiw	16 mg/kg	48	72 %	72 %	0 %
Telfer et al. [46]	IFN-α2b+RBV	3 MU tiw	1,000	24	45 %	63 %	0 %
Harmatz et al. [38]	IFN-α2a+RBV	180 μg/wk	800–1,200	24–48	33 %	ND	23 %
Kamal et al. [a]	PEG-IFN-α2b	1.5 μg/kg/wk		48	46 %	ND	0 %
	PEG-IFN-α2b+RBV		800–1,000		64 %		

[a] Available as abstract only; *IFN* interferon; *RBV* ribavirin; *PEG-IFN* pegylated interferon

has become the most common cause of death in patients with HIV/HCV co-infection. HCV eradication has therefore become a primary goal in co-infected individuals in order to prevent the progression to cirrhosis and development of hepatocellular carcinoma [66].

There have been significant developments in the management of HCV infection during recent years. Combination of peginterferon and ribavirin is the present standard of care in hemophilia patients with HCV infection with SVR rates around 40–60 % resulting in improved quality of life and prolonged survival [49•, 67]. It seems that the natural history of HCV infection as well as the response to anti-HCV therapy of hemophilia patients are similar to those of non-hemophilia patients [49•]. Patients co-infected with HCV and HIV have more risk of developing cirrhosis than HCV mono-infected individuals [68]. The importance of treatment of the HCV infection is highlighted in light of the introduction of effective HAART regimens for suppression of HIV infection. Candidates for HCV therapy should be patients in whom the potential benefits of treatment exceed the potential risks. HIV disease status is a major consideration in this risk/benefit assessment. For patients with relatively high CD4+ cell counts (>350/mL) for whom antiretroviral therapy may be deferred, HCV treatment may be considered. Conversely, patients with low CD4+ cell counts (<200/mL) with untreated HIV infection should not receive HCV therapy until HIV infection is effectively treated [68] and their CD4 counts reach above 200 cells/mL, these patients can be reconsidered for treatment of their HCV infection. HAART regimens should not include zidovudine (AZT) as the use of this drug is contraindicated with ribavirin because of the potential for severe anemia [69]. Co-infected patients have lower SVRs with PEG-IFN and ribavirin treatment compared with mono-infected individuals [70]. The role of the newer oral direct acting antivirals in this patient population remains undefined and the issue of drug–drug interactions in patients on HAART requires careful pre- and post-marketing monitoring. Lastly, non-invasive methods and techniques such as liver transient elastography are increasingly becoming an alternative to liver biopsy and may be preferable in patients with hereditary bleeding disorders [71].

Hemodialysis Patients

Patients on hemodialysis (HD) have a higher prevalence of HCV infection [34]. HCV prevalence in HD varies geographically, both within and between countries [72]. In a meta-analysis from EMRO countries, 32 % of hemodialysis patients were positive for HCV infection and the prevalence ranged from 6 % to 72 % across countries [3•]. Pooled HCV seroprevalence was 17 % in Iran, 63 % in Saudi Arabia, 48 % in Egypt, 72 % in Morocco, and 23 % in Tunisia. Hemodialysis duration, transfusion and previous transplantation failure were major risk factors of HCV infection [3•, 73]. Prevalence of HCV infection has decreased in this group in recent years [74], but still remains a significant public health concern [75]. Overall, chronic hepatitis C patients on hemodialysis have an increased risk of liver-related morbidity and mortality, either while on dialysis or following renal transplantation. HCV-infected patients on HD have significant liver disease and a decreased life expectancy [76]. In addition, the major cause of mortality due to liver failure in kidney transplant recipients is HCV infection [77, 78]. Consequently, treatment of chronic HCV infection should be considered in hemodialysis patients with significant liver disease, minimal other co-morbidities, and when renal transplantation is planned.

At present, pegylated interferon and ribavirin are considered standard treatment in patients with normal kidney function. In patients with end stage kidney disease, PEG-IFN alfa-2a is generally reduced to 135 μg/week and the weekly dose of PEG-IFN alfa-2b is reduced by 50 % [79••] while ribavirin is generally not prescribed because it is not filtered through hemodialysis filters, accumulates in serum, and causes dose-related hemolysis. Only limited data are available about monotherapy with pegylated interferon and combination therapy (PEG-IFN plus ribavirin) for chronic HCV in the dialysis population. Most studies of patients on hemodialysis with HCV infection are small non-randomized prospective studies primarily using conventional interferon. These studies are, for the most part, characterized by low SVR rates and an unfavorable adverse events profile. In a systematic review of the literature and meta-analysis of factors associated with SVR in patients on HD, Alavian and colleagues evaluated 21 studies of 491 IFN-treated patients and 12 studies of 279 PEG-IFN-treated patients. The pooled SVR for standard and pegylated IFN monotherapy in random effects model was 39.1 % (95 % confidence interval [CI], 32.1 to 46.1) and 39.3 % (95 % CI, 26.5 to 52.1), respectively. Pooled dropout rates were 22.6 % (95 % CI, 10.4 to 34.8) and 29.7 % (95 % CI, 21.7 to 37.7), respectively [37]. The odds of SVR were significantly higher for age <40 years than for older patients [80]. A single study by Liu and colleagues compared PEG-IFN-α2a and standard IFN-α2a showing that PEG-IFN-α2a is more effective and safer [80]. Recently, Gordon and coworkers, in an individual patient data meta-analysis, found that women had a significantly higher SVR than men (OR, 2.1; 95 % CI, 1.3 to 3.5), and that a lower baseline HCV RNA was associated with a higher likelihood of SVR (OR, 11.1; 95 % CI, 1.4 to 100; for HCV RNA≤400,000 IU/mL) [81].

Using individualized dosing based on ribavirin plasma levels and hemoglobin concentration, a ribavirin dose of approximately 200 mg/d was determined as optimal in hemodialysis patients [82•]. Rendina and colleagues used this

reduced-dose of ribavirin with PEG-IFN alfa-2a (135 μg/week) in 35 patients, achieving SVR in all 19 patients with non-genotype 1 infection and in 15 of 16 genotype 1 patients. These promising results need to be duplicated in large prospective studies before being recommended for routine use.

Conclusion

HCV remains an important health problem in patients with transfusion-dependent thalassemia, hemophilia and chronic kidney disease patients on hemodialysis in the Middle East and North Africa region. Management of HCV infection demands special attention to comorbidities and a proper risk/benefit assessment. The standard approach for follow-up during therapy with peginterferon and ribavirin is not necessarily applicable to these special groups and response-guided strategies have not been tested. A multidisciplinary approach is often required in this special population in order to properly monitor and manage existing comorbidities as well as treatment-related adverse effects. The new anti-HCV agents, such as the protease inhibitors telaprevir and boceprevir, have been developed for use against HCV genotype 1, significantly increasing the chance of eradication of the virus [83] but their role in special patients such as hemophilia, thalassemia and hemodialysis patients is not clear particularly considering their significant adverse events profile. The development of future interferon-free regimens consisting of direct acting antivirals with pan-genotypic efficacy and favorable adverse events profile is eagerly anticipated perhaps by none more than this special population group with significant unmet needs.

Disclosures No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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