Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Kamal SM. (2011) Hepatitis C virus genotype 4 therapy: progress and challenges. *Liver International*, 31(Suppl-1):45-52.
Date of Review:	February 15, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☐ **Individual** ☒ **Other:** _____ **Target Population:** **hepatitis C virus genotype 4** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Egypt** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☐	☒	☐	Review summary of research studies to provide an overview of the progress and challenges of treatment therapy for hepatitis C genotype 4
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☐	☒	☐	
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				
Efficacy	☐	☒	☐	

Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Studies cited originates from various countries
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☐	☒	
There is evidence of outreach models and case studies to improve access and availability	☐	☐	☒	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☐	☒	☐	No methodology
Are the best practices/methodology/results described applicable in developed countries?	☐	☒	☐	limited data because of low prevalence of HCV genotype 4 in Europe and the United States
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	Most genotype 4 patients reside in the developing countries of Africa and the Middle East
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Liver International*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☐	☐	☐	Free to download from http://onlinelibrary.wiley.com/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☒	☐	Not funded
Other relevant information: _____	☐	☐	☐	- SVR rates in chronic HCV-4 hepatitis are better than those achieve in genotype 1 - Race and ethnicity play a critical

				role in pharmacogenetics and population-level differences in drug response

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Hepatitis C virus genotype 4 therapy: progress and challenges

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Keywords
genotype 4 – hepatitis C – pegylated interferon – ribavirin

Abbreviations
BMI, body mass index; EVR, early virologic response; HCV, hepatitis C virus; HCV-4, hepatitis C virus genotype 4; PEG-IFN, pegylated interferon; RVR, rapid virological response; SVR, sustained virological response.

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Abstract

The hepatitis C virus genotype 4 (HCV-4) is prevalent in Egypt, the Middle East and Africa. Recently, the epidemiology of HCV-4 has changed and this genotype has begun to cross borders and spread to several regions in Europe through immigration and injection drug use. HCV-4 has been considered a difficult-to-treat genotype based on the low sustained virological response (SVR) rates obtained with conventional interferon (IFN)-based regimens. Pegylated interferons (PEG-IFN) plus ribavirin therapy for chronic HCV-4 has been associated with increased SVR rates of more than 60%. Shorter treatment of chronic HCV-4 patients with rapid and early virological responses has been associated with high SVR rates, better compliance, fewer adverse events and lower costs. Despite this progress, the treatment of HCV-4 non-responders, injection drug users, patients coinfected with human immunodeficiency virus, thalassaemic patients, patients on haemodialysis and patients with HCV-4 recurrence after liver transplantation still represents a significant therapeutic challenge. Treatment of HCV-4 has markedly improved, with higher sustained response rates and the possibility of shorter regimens. Despite the recent progress in the treatment of HCV-4, more research is required to optimize current therapy and include genotype 4 patients in clinical trials on emerging therapies such as specifically targeted antiviral therapy for HCV with protease and/or polymerase inhibitors.

Hepatitis C virus genotype 4: shifting epidemiology

Hepatitis C virus genotype 4 (HCV-4) is the most frequent cause of chronic hepatitis C in the Middle East, North Africa and sub-Saharan Africa (1–3). The global epidemiology of HCV-4 is difficult to establish because most epidemiological studies have focused on the prevalence and distribution of HCV-4 in Egypt, the country with the highest worldwide incidence and prevalence of HCV, with rates of up to 13%, where HCV-4 is the cause of 90% of HCV infections (1–8). The prevalence of HCV-4 is 50% in the Kingdom of Saudi Arabia (9, 10), 30% in Syria (11), 76% in the Gaza Strip (12) and 6% in Jordan (13). A few epidemiological studies have described the prevalence of HCV-4 in African countries such as Gabon, Nigeria, Central Africa, Cameroon and Tanzania (14–18).

The HCV-4 has recently spread to Southern Europe through immigration and injection drug use. The prevalence rates of HCV-4 have increased steadily in France (19–21), Italy (22), Greece (23) and Spain (24). In France, the prevalence of HCV-4 increased from 4% in 1990 to more than 11% in a decade (19, 20). In Europe, most HCV-4 cases are clustered among intravenous drug users (19, 21, 23, 24) and patients coinfected with human immunodeficiency virus (HIV) (19–26). A recent study showed that HCV-4 was the second most frequently detected genotype and was found in 23% of a large cohort of HIV-positive homosexual men from England, the Netherlands, France, Germany and Australia (25–27).

Treatment of chronic hepatitis C virus genotype 4-naïve patients

Although approximately 20% of the worldwide HCV population is infected with genotype 4, these patients have been underrepresented in large multicentre clinical trials (28, 29) because of the limited prevalence of this genotype in Europe and the United States. As a result, data regarding the responsiveness of genotype 4 have been limited. The treatment of chronic HCV-4 hepatitis has evolved over the past decade. Initially, conventional interferon (IFN)-α monotherapy administered at a dose of 3–5 MIU three times a week resulted in disappointing sustained virological response (SVR) rates ranging between 5 and 10%. The addition of ribavirin improved the SVR rates to almost 35% (30–33) which were similar to

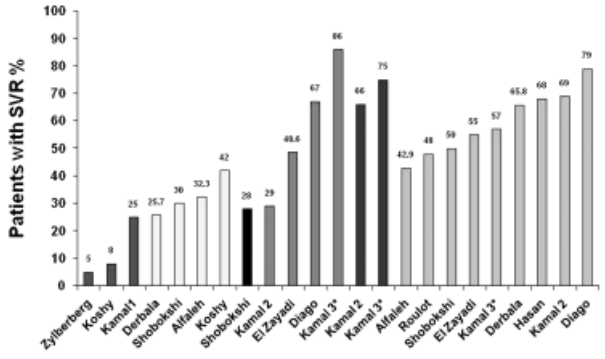

Fig. 1. Evolution of chronic hepatitis genotype 4 therapy. SVR, sustained virological response.

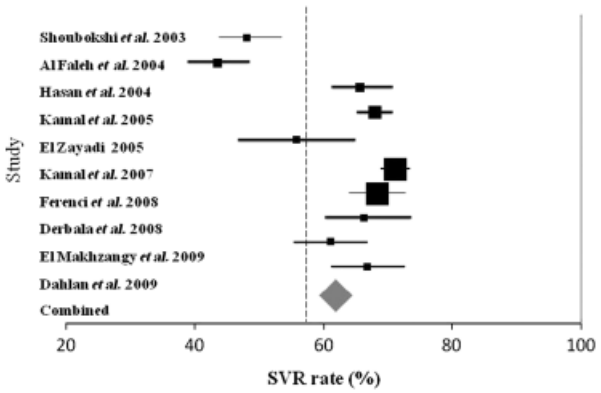

Fig. 2. Meta-analysis of pegylated interferon and ribavirin therapy clinical trials in chronic hepatitis C. SVR, sustained virological response.

SVR in HCV genotype 1 patients but lower than HCV genotype 2 and 3 patients (28, 29). As a result of these SVR rates, HCV-4 was considered a 'difficult-to-treat' genotype.

A steady improvement in the overall response rates of chronic HCV-4 hepatitis to C therapy was achieved with the introduction of pegylated interferon (PEG-IFN)-α2, which resulted in a dramatic improvement in SVR rates compared with conventional IFN-α (34–44) (Fig. 1). A meta-analysis of studies conducted until 2003 that included genotype 4 patients showed significantly higher SVR rates among genotype 4 patients receiving PEG-IFN-α plus ribavirin than in those receiving conventional IFN-α plus ribavirin (55 vs. 30%, $P = 0.0088$) (38). Controlled randomized and non-randomized clinical trials demonstrated high SVR rates ranging between 50 and 79% in chronic HCV-4 hepatitis patients receiving PEG-IFN-α2b plus ribavirin (34–46) (Fig. 2).

Thus, the SVR rates in chronic HCV-4 hepatitis are better than those achieved in genotype 1. The next step in optimizing HCV-4 therapy is to adopt an individualized approach to therapy, adapted to host and viral factors, and to determine the duration of therapy and the therapeutic options for special patient populations.

Tailoring hepatitis C virus genotype 4 therapy

The optimal treatment duration must be defined for successful long-term treatment outcomes using the shortest possible treatment duration to maximize therapeutic efficacy, tolerance and cost effectiveness. Therapy could be individualized by tailoring the drug dosage, intended treatment duration and early stopping rules based on HCV genotype, early viral responses to treatment, pretreatment viral load or body mass index (BMI). Tailoring therapy helps to maximize the benefit of HCV therapy by sparing the patient unnecessary adverse events and the cost of therapy associated with unnecessary treatment. Treatment can also be stopped in patients with unfavourable factors.

Individualization of the duration of therapy based on rapid and early virological response

A shortened course of treatment may be useful when adverse effects or cost is an issue. In an effort to improve SVR rates, various strategies have been adopted to tailor treatment durations based on on-treatment response. The standard duration of therapy for chronic HCV-4 hepatitis was 48 weeks (34–37) until emerging data from randomized prospective trials (39, 40, 44, 45) clarified the optimal duration to identify the determinants of SVR. In one study (39), patients were randomized to receive PEG-IFN-α2b (1.5 μg/kg/week) plus ribavirin (1000–1200 mg/day) for 24, 36 or 48 weeks. Overall, SVR rates were significantly higher in patients receiving treatment for 36 or 48 weeks than in those treated for 24 weeks (66 and 69 vs. 29%, $P = 0.001$ for each comparison). Relapse during follow-up was the highest in patients treated for 24 weeks (20/45, 44%) but relatively rare in the longer treatment arms. There was no significant difference between the 36-week and the 48-week treatment regimens for the overall cohort. Baseline viral load was a predictor of SVR. Patients with pretreatment viral load >2 million copies/ml treated for 24 or 36 weeks had lower SVR rates than those treated for 48 weeks. This suggests that the 48-week treatment regimen may be better suited for patients with high baseline viraemia (Fig. 3).

A non-randomized study (40) compared PEG-IFN-α2b (100 μg/week) plus ribavirin (1000–1200 mg/day) for 24 or 48 weeks. Virological outcomes were similar in patients receiving PEG-IFN-α plus ribavirin for 24 or 48 weeks (SVR, 48.6 vs. 55.0%, $P = 0.517$). However, patients were not randomized but were allocated to the different arms according to the affordability of treatment.

Rapid virological response (RVR), defined as undetectable serum HCV RNA at week 4 of therapy, is becoming an important predictor of the duration of PEG-IFN-α and ribavirin therapy and is a key

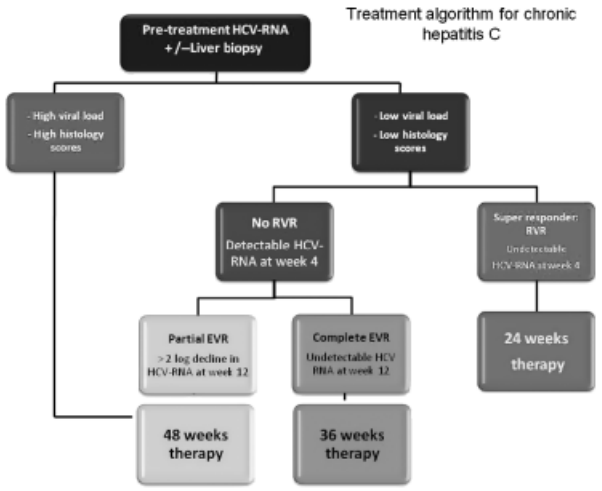

Fig. 3. A proposed algorithm for the treatment of chronic hepatitis C genotype 4. EVR, early virologic response; HCV, hepatitis C virus; RVR, rapid virological response.

opportunity to individualize therapy according to treatment-related viral kinetics (42, 43). Several studies have shown that 24 weeks of therapy is sufficient to induce SVR in patients with chronic HCV-4 patients achieving RVR (44, 45). One study (44) assessed the predictability of response in patients with chronic HCV-4 infection and determined the efficacy of a variable shorter-duration PEG-IFN-α2b plus ribavirin treatment regimen based on viral load at weeks 4 and 12. Participants were randomly assigned to receive treatment either for the standard fixed duration of 48 weeks (control group, $n = 50$) or a shorter treatment based on interim viral load. In patients with chronic HCV-4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN-α2b and ribavirin for 24 weeks and 36 weeks, respectively, yielded high SVR rates with significantly fewer adverse events and better compliance. After controlling for predictors, low baseline histological grade and stage were associated with SVR ($P < 0.029$) in all groups. In addition, in patients treated for 48 weeks, older age ($P = 0.04$), higher baseline BMI ($P = 0.013$) and low baseline HCV RNA ($P < 0.001$) were also associated with SVR. Overall, these data suggest that in patients with chronic HCV-4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN-α2 and ribavirin for 24 weeks and 36 weeks, respectively, is sufficient.

Another study (45) reported an SVR rate of 86.7% [95% confidence interval (CI): 69.3–96.2%] in patients infected with HCV-4 who were assigned to 24 weeks of treatment with PEG-IFN-α2a 180 mug/week plus ribavirin 1000/1200 mg/day after achieving a RVR. This prospective study also confirms that a 24-week regimen of PEG-IFN-α2a plus ribavirin 1000/1200 mg/day is appropriate in genotype 4 patients with a low baseline HCV RNA level who achieve an RVR by week 4 of therapy.

Recently, the combination of nitazoxanide, PEG-IFN-α2a and ribavirin increased the percentage of patients with RVR and SVR, compared with patients given PEG-IFN plus ribavirin, without an increase in adverse events (47). The addition of nitozoxanide to standard of care helped increase SVR rates and shorten the treatment duration to 24 or 36 weeks. Given the adequate safety profile of nitazoxanide and the reasonable cost of this oral therapy, the short duration of triple therapy with pegulated interferon (PEG-IFN), ribavirin and nitazoxanide could be a cost-effective regimen for chronic HCV-4 hepatitis.

Pharmacogenetics, race, ethnicity and personalized medicine for hepatitis C virus therapy

Race and ethnicity play a critical role in pharmacogenetics and population-level differences in drug response. Certain studies have demonstrated that in non-responders, some IFN-stimulated genes were upregulated before treatment (48–51). These findings associated with clinical, biochemical and histological data may help detect potential non-responders before starting treatment. This is an important issue since the standard treatment is physically demanding and costly. The aim of pharmacogenetics is to identify the individual genetic determinants of drug activity so that therapy can be tailored to the individual patient. It has been shown that certain ethnicities such as African Americans, Hispanics and Asians might respond differently to HCV therapy.

Currently, it is not clear whether patients with chronic HCV-4 respond differently to PEG-IFN-α and ribavirin therapy. A retrospective analysis of SVR rates in French, Egyptian and African patients with chronic HCV-4 showed an overall better response in Egyptian patients infected with the 4a subtype (52). In multivariate analysis, two factors were independently associated with SVR: an Egyptian origin of transmission and the absence of severe fibrosis. It is not clear from this study whether the difference in SVR was related to ethnicity, HCV-4 subtype or the mode of transmission. Egyptian patients acquired the infection through antischistosomal therapy, while most of the French and African patients acquired the infection through illicit drug use. Another study (53) showed that treatment of patients with chronic HCV-4 infection by PEG-IFN-α2b and ribavirin results in a more rapid decrease in HCV RNA level and a better SVR rate (62 vs. 13%) in Egyptians than in non-Egyptians. In contrast, a Spanish study (54) evaluating the response of chronic HCV-4 treatment-naïve Spanish patients to combination therapy revealed a SVR of 55%. Patients infected with HCV-4 had a lower stage of fibrosis, lower viraemia and a higher SVR rate compared with those with genotype 1.

Despite these interesting observations, it is not known why Egyptians infected with HCV-4 respond better to therapy than chronic HCV patients in the West or sub-Saharan Africa. The difference could be due to the mode

of infection because genotype 4 infection is prevalent in special populations in Europe and sub-Saharian Africa namely injecting drug users, HIV-coinfected and homosexual men, all of whom have been identified in several studies as difficult-to-treat groups.

The variations in response to HCV therapy could be because of different pharmacogenetics because individual genetic make-up could influence the individual response, resistance to therapy or the development of potential side effects. Identifying individuals with a high probability of response or upfront resistance to therapy, determining the probability of adverse events and understanding how certain individuals metabolize drugs are the basis of *personalized medicine*. Some studies have identified genetic variations in the *IL28B* gene (coding for IFN-λ3) that determines the outcome of IFN-α-based therapy for patients with genotype 1 chronic HCV infection (49, 50). This polymorphism is located within the promoter of *IL28B* and several independent genome-wide association studies reported SNPs in the *IL28B* region, associated with response to treatment (48–50). The exact mechanisms underlying this association are unknown (52). It has been shown that in non-responders, some IFN-stimulated genes were highly expressed; thus, preactivation of the IFN system in patients appears to limit the effect of IFN antiviral therapy (51, 52) However, the link between genetic polymorphisms and IFN response is not clearly established.

This finding could help develop personal treatment options in patients with chronic HCV infection and explain some of the apparent genetic differences in response to treatment, for instance in African Americans, Asians or Hispanics. Testing the patient's genotype to determine how likely they are to respond to anti-HCV therapy would be a major step in personalized medicine.

Tailoring hepatitis C virus therapy and financial constraints

Many genotype 4 patients reside in the developing countries of Africa and the Middle East, where delivery of quality health care is often limited by lack of resources, and economic constraints frequently prevent adequate treatment intervention. For example, in Egypt, despite the government's nationwide campaign for treating patients with chronic HCV infection, certain patients may not have adequate health insurance coverage or access to treatment. Thus, the person's financial status often plays a major role in poor compliance and many patients cannot afford to complete a full course of therapy with PEG-IFN plus ribavirin (41).

Recent studies have suggested that the PEG-IFN and ribavirin regimen will probably be replaced by the addition of specifically targeted antiviral therapy for HCV (STAT-C). However, these antivirals will probably not be available in the near future in regions with a high prevalence of HCV genotype 4 for several reasons. Firstly, none of the clinical trials on new HCV drugs have enrolled enough patients with HCV-4 infection to test the efficacy and duration of a new regimen for chronic HCV-4 hepatitis although the HCV genotype significantly influences therapy. Secondly, resistance to new antivirals such as HCV protease inhibitors and the potentially resistant strains of HCV are likely to develop. Thirdly, the new antivirals are used in combination with the standard of care, leading to a significant increase in the cost of therapy. Therefore, it is important to test the efficacy of direct antiviral combinations in areas in which the HCV genotype 4 predominates.

Thus, determining the safe therapeutic regimen that induces high SVR rates is paramount to restrict the transmission of HCV, halt the progression of chronic hepatitis and provide cost-effective treatment, because this regimen will reduce the cost of care in patients with end-stage liver disease and hepatocellular carcinoma. In Egypt and the Middle East, no adequate economic evaluation of the available therapeutic regimen for hepatitis C has been conducted thus far. However, as new therapeutic approaches become available, economic evaluation studies are critical to maximize the cost benefit of available combinations. This is particularly important in developing countries and countries with a high prevalence of HCV such as Egypt, where HCV infection is a major public health problem and a heavy economic burden. An economic evaluation is important to identify, measure and evaluate a wide range of therapeutic alternatives. This can provide decision makers with necessary information about the cost effectiveness of therapeutic options.

Treatment of non-responders

Treatment of non-responders is a challenge in all genotypes. Management of chronic HCV-4 hepatitis patients who do not respond to IFN therapies has only been studied in one small trial (54) on the efficacy and safety of PEG-IFN plus ribavirin with or without amantidine in 63 non-responders to conventional IFN therapy. Patients were randomized to receive either weekly PEG-IFN-α2b, 1.5 μg/kg and ribavirin 1000–1200 mg or PEG-IFN and ribavirin as in group A, plus amantadine. Only one patient (5%) treated with dual therapy and three patients (7%) treated with triple therapy achieved SVR. Further clinical trials are necessary to investigate the management options for this population.

Treatment of chronic hepatitis C virus and human immunodeficiency virus coinfections

Although in Europe, HCV-4 is frequent among HCV- and HIV-coinfected patients, few clinical trials have evaluated the efficacy of PEG-IFN and ribavirin therapy in patients with HIV and HCV-4 coinfection (55–57). In a case series study, SVR rates of 16.7% were obtained in genotype 4 patients receiving various IFN-based antiviral therapies (55). Overall, SVR was

attained in 11.1% of patients receiving IFN-α monotherapy, 9.1% of patients receiving IFN-α plus ribavirin combination therapy and 22.7% of patients receiving PEG-IFN-α2b (1.5 μg/week) plus ribavirin (800 mg/day). In this study, the overall SVR rates in genotype 4 patients (16.7%) were similar to those achieved by genotype 1 patients (11.2%) and lower than those in genotype 2/3 patients (40.4%).

In another study, end of treatment response and SVR rates were lower in HIV/HCV-coinfected patients than in HCV-monoinfected patients (30 vs. 66%, $P = 0.06$; 15 vs. 50%, $P = 0.06$ respectively) receiving PEG-IFN-α plus ribavirin (1000–1200 mg/day) for 48 weeks; the difference between the cohorts was not significant in either case. The SVR rates of $< 20\%$ reported in coinfected patients are clearly lower than those reported in HCV-monoinfected genotype 4 patients receiving combination therapy with PEG-IFN-α plus ribavirin (50–79%) (56).

A recent Italian Spanish study (57) assessed the efficacy of PEG-IFN and ribavirin therapy in 75 HCV-G4 patients coinfected with HIV. The overall SVR was 28% in Spanish and 34% in Italian HCV-4 patients respectively. These studies suggest that coinfected HCV-4 patients can be considered to be a difficult-to-treat population.

Treatment of acute hepatitis C virus genotype 4

A few clinical trials have addressed the optimal treatment regimen in acute HCV-4 infection and have shown high SVR with IFN-based therapies compared with no treatment (58–60). These studies have shown that patients with acute HCV-4 infection have higher rates of SVR than genotype 1 patients. The SVR rates in acute HCV genotype 4 patients reached 93 and 100% compared with 60 and 88% in genotype 1 patients after 12 and 24 weeks of treatment respectively (59).

Treatment of thalassaemia major patients with chronic hepatitis C virus infection genotype 4

Although many thalassaemia patients are infected with HCV, the treatment of these patients has not been established. A randomized study (61) evaluated the efficacy of PEG-IFN-α with or without ribavirin in 20 patients with thalassaemia and HCV-4. SVR occurred in four of 12 and five of eight patients in the monotherapy and combination groups (30 and 62.5%, $P = 0.19$) respectively. Transfusion requirements increased by 34% in the combination arm ($P = 0.08$). In another study (62), overall SVR rates were 46% with PEG-IFN-α2b and 64% with PEG-IFN-α2b+RBV combination therapy. However, adverse events and withdrawals were more frequent with PEG-IFN-α2b+RBV combination therapy than with PEG-IFN-α2b alone. Combination therapy was associated with a temporary increase in transfusion requirements.

Predictors of sustained virological response in chronic hepatitis C virus genotype 4

Some studies have evaluated the predictors of SVR in HCV-4. Rapid virological response has been established as an excellent predictive factor of SVR (44–47). Recent studies (63, 64) showed that RVR proved to be the most sensitive on treatment parameter for predicting SVR identifying 96% of subjects likely to develop SVR. RVR was also shown to have excellent specificity (98%), discriminating between subjects who will probably go on to achieve SVR from those who will not. RVR misses only a fraction of the subjects who do not achieve SVR because of the very high negative predictive value and positive predictive value of RVR (96 and 97% respectively).

Jessner *et al.* (65) studied very early viral kinetics on IFN treatment in chronic HCV-4 infection by measuring viral load before and 24 h after 10 MU IFN-α2b. The study showed that a 24-h log 10 change after 10 MU IFN-α2b could be a good predictor of SVR on PEG-IFN-α2a/RBV combination therapy. This test may be useful to identify probable non-responders to PEG-IFN-α/RBV therapy in genotype 4 patients.

Among the baseline criteria, one study showed that a low baseline histological grade and stage ($P < 0.029$), BMI ($P = 0.013$) and HCV RNA ($P < 0.001$) were significantly associated with SVR (43). Similarly, another study found a significant association between SVR and severe fibrosis (Metavir score $>$ F2) [odds ratio (OR) = 0.4, 95% CI: 0.2–0.8] as well as the presence of steatosis (OR = 0.5, 95% CI: 0.3–0.97) (43).

Moderate to severe steatosis with or without sinusoidal fibrosis is present in about 70% of patients with genotype 4 chronic hepatitis C (43). Advanced fibrosis and steatosis have been associated with lower SVR rates (43). Two studies (66, 67) reported that the treatment outcomes were improved in genotype 4 patients with mild liver disease compared with those with more advanced liver disease. In patients receiving PEG-IFN-α2b plus ribavirin (1000–1200 mg/day) for 48 weeks, the SVR rates were significantly higher in those without or with mild fibrosis (84 vs. 29%, $P < 0.0002$). Another study showed that SVR was independently associated with HOMA-IR < 2 ($P = 0.001$, OR = 5.314, 95% CI: 1.953–14.459) and non-severe fibrosis ($P < 0.001$, OR = 8.059, 95% CI: 2.512–25.855) (64).

Emerging new regimen for the treatment of chronic hepatitis C virus genotype 4

A phase II, randomized, double-blind, placebo-controlled study of nitazoxanide treatment for 24 weeks in 50 patients with chronic HCV-4 hepatitis was performed to evaluate the safety of prolonged administration and to determine the antiviral efficacy of nitazoxanide monotherapy (46). This study sequentially allocated 97 Egyptian patients with chronic HCV-4 hepatitis into three treatment arms: PEG-IFN-α2a and ribavirin for 48 weeks

($n = 40$), nitazoxanide monotherapy for 12 weeks, followed by nitazoxanide plus PEG-IFN α-2a for 36 weeks ($n = 28$), or nitazoxanide monotherapy for 12 weeks, followed by nitazoxanide plus PEG-IFN-α2a and ribavirin for 36 weeks ($n = 28$).

The percentages of patients with RVR and SVR were significantly higher in patients receiving triple therapy than in those receiving the standard of care (64 vs. 38%, $P = 0.048$ and 79 vs. 50%, $P = 0.023$ respectively). Patients given nitazoxanide plus PEG-IFN-α2a had intermediate rates of RVR (54%) and SVR (61%). Adverse events were similar across treatment groups, except for a higher rate of anaemia in the groups receiving ribavirin. In the nitazoxanide group, virological responses were maintained through the end of treatment with no virological breakthroughs. Of note, the use of nitazoxanide was associated with reduced relapse rates (3/20 patients in the PEG-IFN plus nitazoxanide arm and 1/23 patients in the triple arm with PEG-IFN, ribavirin and nitazoxanide) vs. 10/30 patients in the standard-of-care arm.

Conclusions and future prospects

Hepatitis C virus genotype 4 is responsible for about 20% of hepatitis C infections worldwide. HCV-4 is rapidly spreading to the West through immigration and injection drug use. Recent clinical data have provided new insights on HCV-4 infection and helped to refine treatment strategies. These data can now be used as a platform for optimizing treatment regimens for patients infected with HCV-4. Further research is needed to investigate the response of HCV-4 infections to emerging therapies such as STAT-C in particular protease and/or polymerase inhibitors.

Conflicts of interest

The author has declared no potential conflicts.

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