Antiviral treatment of hepatitis C virus infection and factors affecting efficacy

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Abstract

Hepatitis C virus (HCV) infection is the leading cause of chronic liver-related diseases, including cirrhosis, liver failure, and hepatocellular carcinoma. Currently, no effective vaccine is available for HCV infection. Polyethylene glycol interferon-α (PegIFN-α) in combination with ribavirin (RBV) is the standard care (SOC) for chronic hepatitis C. However, the efficacy of PegIFN-α and RBV combination therapy is less than 50% for genotype 1 HCV, which is the dominant virus in humans. In addition, IFN and RBV have several severe side effects. Therefore, strategies to improve sustained virological response (SVR) rates have been an important focus for clinical physicians. The serine protease inhibitors telaprevir and boceprevir were approved by the United States Food and Drug Administration in 2011. The addition of HCV protease inhibitors to the SOC has significantly improved the efficacy of treatments for HCV infection. Several direct-acting antiviral drugs currently in late-stage clinical trials, both with and without peg-IFN and RBV, have several advantages over the previous SOC, including higher specificity and efficacy, fewer side effects, and the ability to be administered orally, and might be optimal regimens in the future. Factors affecting the efficacy of anti-HCV treatments based on IFN-α include the HCV genotype, baseline viral load, virological response during treatment, host IL28B gene polymorphisms and hepatic steatosis. However, determining the effect of the above factors on DAA therapy is necessary. In this review, we summarize the development of anti-HCV agents and assess the main factors affecting the efficacy of antiviral treatments.

Core tip: Understanding the effectiveness and affecting factors of antiviral regimens are critical for making informed treatment decisions for hepatitis C virus (HCV) infection. In this review, we have summarized the history of anti-HCV agents from interferon to the direct-acting antiviral drugs (DAAs) without polyethylene glycol interferon-α therapies and the affecting factors of antiviral treatment, focusing on investigating the optimal combination of antiviral therapies to achieve higher efficacy and better medication compliance. Although the efficacy of DAAs is significantly improved, many unmet needs and questions remain, such as avoidance of cross-resistance, the remaining high incidence of side effects, the role of IL28B status as well as the management of patients who do not respond to therapy.

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INTRODUCTION

Hepatitis C virus (HCV) infection, a worldwide public health problem affecting 170 million patients, is likely the cause of chronic hepatitis, liver cirrhosis, liver failure, and hepatocellular carcinoma[1]. Of the patients with chronic HCV infection, 40%-75% still exhibit extrahepatic manifestations including metabolic, hematological, vascular and rheumatological diseases[2,3]. Until recently, however, there have been no effective vaccines available. In the early 2000s, polyethylene glycol interferon-α (PegIFN-α) combined with ribavirin (RBV) became the standard of care (SOC) regimen for HCV, which showed a SVR that was mainly associated with its genotype. For example, patients with genotype 1 achieved a sustained virological response (SVR) of less than 50%. Additionally, this treatment regimen has several side effects, including granulocytopenia, anemia, and depression, and it is associated with a long treatment duration and increased cost.

In 2011, the first direct-acting antiviral drugs (DAAs), telaprevir and boceprevir, were approved by the United States Food and Drug Administration (FDA). Combined with PegIFN-α and RBV, these DAAs resulted in a higher SVR rate in patients with HCV genotype 1. Thus, this treatment regimen became the SOC regimen for such patients. Soon afterward, other DAAs in the pre-clinical or pilot phase also achieved good treatment results. Current studies are focusing on investigating the optimal combination of antiviral therapies to achieve higher efficacy, shorter treatment duration, more simple administration, and better medication compliance. In response to an approved DAA, an evaluation of multiple factors (HCV genotype, baseline viral load, virological response during the treatment, and IL28B gene polymorphisms) affecting anti-HCV treatment based on IFN is necessary.

ADVANCES IN ANTIVIRAL TREATMENT

Interferon

PegIFN-α: When administered as a once-a-week injection, PegIFN-α increased the SVR rate and compliance in patients by delaying renal clearance to extend the in vivo half-life by cross-linking polyethylene glycol and interferon-α. Currently, treatment combining PegIFN-α and RBV is still the most widely used SOC regimen.

Many clinical studies have compared the SVR rates in patients receiving different PegIFN-α (e.g., IFN-α-2a and IFN-α-2b), dosages, and treatment durations. The results suggested that the patients given a standard dose (180 μg) of PegIFN-α-2a had higher SVR rates than those given a weight-based dose (1.5 μg/kg) of PegIFN-α-2b[4]. The IDEAL study, which included 3070 patients with hepatitis C, showed that the SVR rate in patients with HCV genotype 1 infection given different doses of PegIFN-α-2b (1.0 or 1.5 μg/kg) was not different from that in patients given PegIFN-α-2a (180 μg)[4]. In patients with HCV genotype 2/3 infections, those given a standard dose of PegIFN-α-2b (1.5 μg/kg) had a higher SVR rate than those given a low dose[4,5]. Meanwhile, the SVR rates in patients receiving a high dose of RBV (1000-1400 mg/d) were higher than those in patients receiving a low dose (800 mg/d) of the PegIFN-α-related treatments[6,14]. The difference was especially obvious in the patients with a genotype 1 infection. Some studies investigated the antiviral therapy administered to patients with a genotype 2/3 infection. Although the overall SVR rate decreased after shortening the duration, a 12- or 16-wk treatment period was recommended for patients who achieved rapid virological responses (RVR)[10,13,16].

Human serum albumin IFN-α fusion: Albinterferon is a genetic fusion protein used for the treatment of chronic hepatitis C (CHC), which takes advantage of the long half-life of human albumin to provide a new treatment approach that enables albinterferon administration at 2- or 4-wk intervals in individuals with CHC. Studies have demonstrated that the SVR rate resulting from the combined treatment of albinterferon and RBV was equivalent to that resulting from the SOC treatments, and the incidence rates of adverse drug reactions were also similar[7,10]. However, albinterferon is associated with the risk of reduced lung function, particularly in patients being treated for more than 6 wk[10].

PegIFN-λ-1a: IFN-λ is a class III interferon and has completely different receptors from those of IFN-α, RIG-I. Its receptors are mainly distributed in the liver, which means that the extrahepatic adverse reaction from IFN-λ is significantly reduced compared with that from IFN-α. In recent years, PegIFN-λ-1 has been confirmed to have anti-HCV activity and mild adverse reactions[28]. One clinical trial assessed the efficacy and safety of PegIFN-λ-1a plus RBV compared to the SOC for the treatment of naïve patients with HCV genotypes 2/3. The results showed that the curative effects of the two treatments were similar but that the viral load in the PegIFN-λ-1a group decreased faster and that the adverse reactions were significantly reduced[29].

DAAs

NS3 protease inhibitors: The unique structure and function of NS3 protease in the HCV life cycle makes it a new target for anti-HCV drug development. In addition to cleaving the polyprotein and generating the NS3, NS4A, NS4B, NS5A, and NS5B proteins, NS3 protease acts as an antagonist of the host innate immune system by cleaving signaling molecules that mediate a cellular antiviral response and resulting in the suppression of interferon production. The two NS3 protease inhibitors...
discussed herein are telaprevir and boceprevir.

Telaprevir, as the first approved DAA, has a recommended dose of 750 mg tid, combined with PegIFN-α and RBV treatment (triple therapy), for a duration of 48 wk for naïve or previous treatment failure HCV genotype 1 patients. The disadvantage of this medication is the need to ingest it with greasy food, which may cause an incredible weight increase during treatment. Six randomized clinical trials assessed the efficacy of the triple therapy compared with the SOC in naïve HCV genotype 1 patients[22-27]. All patients were treated with telaprevir, PegIFN-α, and RBV for 8 or 12 wk, followed by the combined therapy of PegIFN-α and RBV. The results showed that the telaprevir triple therapy for 24 wk yielded a higher SVR rate than the SOC[22,24-26]. Even when the duration was shortened to 12 wk, the SVR rates were equivalent to those of the SOC[28], but prolonged duration did not improve its efficacy for those who achieved rapid virological response (RVR) and early virological response (EVR)[26,27]. The administration frequency of telaprevir (750 mg tid or 1125 mg bid) and PegIFN type (α-2b or α-2a) in patients with RVR and EVR had no effect on the SVR rate[23]. Among the previous treatment failure patients, the telaprevir triple therapy group had a higher SVR rate than that of the SOC group, but the overall effect was poor, especially for non-responders, with an SVR rate of 29%-33%[29]. Common adverse reactions to telaprevir include anemia, rash, nausea, hemorrhoids and itching. Because telaprevir treatment can lead to resistant mutants over the short term, the long-term use of the drug should be limited. Drug resistant mutants have been found to exhibit the following changes: V36A/M, T54A/V, and R155K/T, and A156S/T.

Boceprevir is another NS3 protease inhibitor approved at the same time as telaprevir. The recommended dose of boceprevir is 800 mg tid, combined with PegIFN-α and RBV therapy, for a duration of 48 wk for naïve or previous treatment failure HCV genotype 1 patients. Unlike telaprevir, boceprevir is started at week 4 of treatment, following a 4-wk lead-in period of treatment with peg-IFN and RBV, and RBV is required to enhance the efficacy of boceprevir[29]. Studies showed that the boceprevir triple regimen among naïve patients for 48 wk increased the SVR rate associated with the SOC treatment to 16%-37%[30,31] whereas the SVR rates in the previous treatment failure patients were significantly higher (59%-66% vs 21%)[32]. Boceprevir-related adverse effects include fatigue, anemia, nausea, headache, dry mouth, granulocyte decreases, taste disorders, and thrombocytopenia. The long-term use of this drug can also lead to resistance mutations, including V36A/M, T54A/S, V55A, R155K/T and A156S/T/V.

Simeprevir is a second-generation NS3 protease inhibitor and a competitive reversible macro cyclic, noncovalent inhibitor of NS3/4A protease[33]. Phase II clinical trials compared the efficacy of simeprevir, PegIFN-α and RBV with the SOC treatment for naïve or previous treatment failure HCV genotype 1 patients. Among the naïve patients, those treated with the triple therapy with different doses of simeprevir (75 or 150 mg) once a day (qd) for 12 or 24 wk and then with PegIFN-α and RBV, for a total treatment course of 24 or 48 wk, obtained a higher SVR ratio compared with that of patients treated with the SOC (74.7%-86.1% vs 64.9%). In addition, for the majority of patients, the duration can be shortened to 24 wk[34]. The phase II b ASPIRE study demonstrated that simeprevir is a highly potent, efficacious, and well-tolerated once-daily PI for the majority of prior null or partial responders and relapers compared to IFN-based therapy. Simeprevir has entered a phase III clinical study. The most common adverse reactions are nausea, fatigue and hyperbilirubinemia, which are generally mild and reversible. The resistance mutations include Q80K and R155K.

Faldaprevir is a second-generation HCV NS3/4A protease inhibitor. Phase II clinical trials have compared the efficacy of the SOC with that of the combined treatment with faldaprevir, PegIFN-α, and RBV in treatment-naive or treatment-experienced patients with chronic hepatitis C genotype 1 infection. The SVR rate in the treatment-naive patients who underwent 24-wk triple therapy including faldaprevir 240 mg qd with no lead-in was the highest, at up to 84%, whereas the group receiving the same drug dose with lead-in during the early phase of treatment or receiving a half dose of faldaprevir had a 72% SVR; in contrast, the other group (SOC regimen) had a SVR of only 56%[35]. Similar results were obtained for the treatment-experienced patients. The group receiving triple therapy with faldaprevir 240 mg qd for 48 wk with no lead-in had the highest SVR rate (50% in prior partial responders and 35% in prior null responders); the SVR rate in the lead-in treatment group that received the same dose was the lowest[35]. The adverse responses of faldaprevir include jaundice, skin changes (e.g., rash), photosensitivity, pruritus, nausea, vomiting, diarrhea, and dryness. The incidence of side effects is associated with the dosage. To date, the resistance mutations R155K and D168V/E have been observed.

Danoprevir is another second-generation NS3 protease inhibitor used for the treatment in naïve or experienced HCV genotype 1 patients, and it is expected to eliminate the use of IFN-based drugs. One clinical trial compared the efficacy of the SOC with that of the combined treatment with danoprevir, PegIFN-α and RBV in treatment-naive patients with HCV genotype 1 infection[37]. The SVR rate in the group given danoprevir 600 mg q12h was the highest at up to 85%, whereas the group receiving the SOC had a SVR rate of 42%. Even when the duration among patients given danoprevir who had an extended rapid virological response (eRVR4-20: HCV RNA < 15 IU/mL during weeks 4-20) was shortened to 24 wk, 96% had an SVR. The INFORM-1 study evaluated the combination of danoprevir and mericitabine. Combination therapy was administered for up to 2 wk, resulting in a reduction in viral load and undetectable HCV RNA levels at the end of dosing in 63% of
treatment-naive patients\cite{36}. Relevant evidence indicates that ritonavir can inhibit the metabolism of danoprevir \textit{in vivo}, reduce the side effects, and improve the SVR rate, providing the possibility for IFN-free combination therapy. The INFORM-SVR study provided SVR data for the combination of mericitabine and danoprevir/ritonavir with or without RBV for 12-24 wk. SVR rates in HCV genotype 1a and genotype 1b patients were 26% and 71% in treatment arms including RBV, respectively, but significantly lower SVR rates were found in all RBV-free treatment groups\cite{35}. The adverse reactions of danoprevir mainly include anemia, neutropenia, and rash. The resistance mutations R155K and D168T/E have been observed.

ABT-450 is a potent, specific protease inhibitor of HCV NS3. Ritonavir is used to increase the plasma concentration of ABT-450, prolong its half-life, and reduce the risk of drug resistance, enabling an ABT-450 dose regimen of once daily\cite{33,34}. Fifty HCV genotype 1 patients including naive, prior partial or null responders participated in an open-label, multiple-center phase II ABT-450 clinical trial. In the application of the combined treatment of ABT-333 [non-nucleoside inhibitors (NNI)], RBV, and ritonavir, the curative effects of different doses of ABT-450 over 12 wk were assessed. The results suggested that the SVR rates were higher than 90% in treatment-naive patients and 47% in prior partial or null responders\cite{34}. The common adverse responses of ABT-450 include fatigue, pain, hyperbilirubinemia, and vomiting.

There are many other NS3 protease inhibitors in clinical studies, such as asunaprevir (BMS 650032), vaniprevir (MK-7009), narlaprevir (SCH 900518), VX 985, and MK-5172. Some of these NS3 protease inhibitors are expected to be approved for anti-HCV therapy in the near future.

**NS5A inhibitors:** NS5A is an essential viral component of the membrane-associated HCV replication complex and plays an important role in the formation of HCV infectious particles. Daclatasvir (BMS) 790052 was the first-in-class NS5A-specific targeted molecular inhibitor to be developed. Preclinical studies have shown that this NS5A inhibitor has broad genotype antiviral activity, but the associated mechanism is unclear. A phase IIa study compared the efficacy of the combination of daclatasvir and asunaprevir (two-drug treatment) with or without the addition of PegIFN-α and RBV for the treatment of HCV genotype 1 prior null responders over a 24-wk duration. The results showed that the sustained virological response at post-treatment week 14 (SVR24) of the two-drug treatment was 36% and that the sustained virological response at post-treatment week 12 (SVR12) and SVR24 of the four-drug treatment were 100% and 90%, respectively\cite{41}. High virological response rates were obtained in 90 treatment-naive patients administered the combination of daclatasvir with sofosbuvir, with or without RBV, for 24 wk. In HCV genotype 1 patients, RVR and SVR rates were 100% and 100%, while in HCV genotype 2 and genotype 3 patients they were 100% and 91%, respectively\cite{41}. However, it is notable that all failures were relapses after therapy. Analyses of resistance \textit{in vivo} and \textit{in vitro} showed mutations in the amino acid residues L31V/M and Y93H/N.

Several other NS5A inhibitors have also entered clinical trials, including ABT-267, ledipasvir (GS-5885), ACH-2928, and IDX791. Some of these inhibitors may be approved to become anti-HCV drugs.

**NS5B polymerase inhibitors:** NS5B is an RNA-dependent RNA polymerase (RdRp) in the HCV replication complex that catalyzes the synthesis of positive- and negative-stranded viral RNAs. Because mammals lack RdRp, new drugs to act as HCV NS5B polymerase inhibitors will be highly specific. NS5B enzyme activity can be inhibited by different types of compounds: nucleoside/nucleotide derivative inhibitors (NIs) and NNIs. NIs can competitively bind to RdRp active sites, whereas NNIs target allosteric enzyme binding sites. Therefore, because both classes of drugs affect RdRp at different sites, cross-resistance is not easily produced.

NIs can simulate natural polymerase nucleotide substrates and act as a terminator that can be incorporated into RNA. The highly conserved HCV RdRp activation center showed that NIs have a similar efficacy on different HCV genotypes, as well as a high barrier to and low incidence of resistance genes.

Sofosbuvir can be used for the treatment of non-genotype 1 HCV infection\cite{47,48}. A randomized, double-blind phase II clinical trial showed that treatment with sofosbuvir, PegIFN-α, and RBV for 12 wk, followed by subsequent treatment with PegIFN-α and RBV for 12 or 36 wk, resulted in a SVR12 rate of 90% in HCV genotype 1 patients, which was similar to that in genotype 2/3 patients (92%)\cite{48}. Another clinical trial showed that the 12-wk treatment of HCV genotype 1 naive patients with sofosbuvir, PegIFN-α and RBV was safe and effective. In addition, extended duration did not improve the efficacy, although these results need to be further confirmed by phase III clinical trials\cite{48}. It is notable that no viral breakthrough or resistance development during therapy has been described. Because of the absence of cross-resistance with the other DAA, including NS5A inhibitors, sofosbuvir can be used for salvage therapy.

**Mericitabine** is a nucleoside analog polymerase inhibitor of HCV. Phase II clinical study data showed that the treatment with mericitabine combined with PegIFN-α and RBV was safe and well tolerated. In the triple regimen for 24 wk, the SVR rate in HCV genotype 1/4 treatment-naive patients was higher than the SOC group\cite{46}. The phase II MATTERHORN study showed that for genotype 1a/1b prior null and partial responders after the combined treatment with ritonavir, danoprevir, mericitabine, PegIFN-α and RBV, the sustained virological response at post-treatment week 4 (SVR4) reached 83% and 100%, respectively. Currently, resistance mutants have not been found.

The design of NNIs involves targeting one of at
least five non-contiguous sites of RdRp allostERIC enzymes, resulting in conformational changes that inhibit the enzyme activity, which have limitations on the geno-
type compared with NIs. A low genetic barrier may soon induce virus mutations. In phase I and II clinical-
studies, the results showed that BI 207127 and VX-222, re-
gardless of whether they were combined with PegIFN-α
treatment, can both improve the genotype 1 HCV
infection RVR or EVR rate and demonstrate good tole-
rance. However, reducing the treatment with PegIFN-α
resulted in a relatively high proportion of virological
breakthroughs[47-49].

Cyclosporine - a cyclophilin inhibitor: Cyclophilins
are a family of cell isomerases, including cyclophilins A,
B, and C. The importance of human cyclophilins in HCV
replication was confirmed by the anti-HCV activity of cy-
closporine A. The mechanism of action of cyclosporine
A involves NS5A and/or NS5B. Alisporivir (Debo-025)
is a derivative of cyclosporine A, which removed the
immunosuppressive activity but retained the potent antiviral
activity against a wide range of HCV genotypes. All cy-
clophilin inhibitors have a high barrier to resistance. In
vitro studies have shown a lack of significant cross-resis-
tance with NS3/4A or other protease inhibitors. More-
over, there is an additive effect when cyclophilin inhibi-
tors are combined with PegIFN-α. Thus, in addition to
having the advantage of once-daily administration, these
agents are promising host-directed antivirals[50,51].

Supplementation therapy: In vitro, vitamin B₂ acts as
a natural inhibitor of HCV replication. A study assessed
the effect of vitamin B₂ on the virological response in antiviral therapy-naïve patients with chronic HCV in-
fec tion. The SVR rate was significantly higher in the SOC
plus B₂ group than in the SOC group[52]. At present, it
is also believed that vitamin D has an anti-HCV activity
in vitro that is mediated through its active metabolite,
calcitriol[53]. The SVR of treatment-naïve patients with
chronic HCV genotype 1 or 2/3 infection is signifi-
cantly improved by adding vitamin D to conventional
PegIFN-α and ribavirin therapy[54,55]. However, given the
very small number of available studies, additional studies
are needed to assess potential differences in the associa-
tions between vitamin B₂/vitamin D and SVR for HCV.

The hematologic adverse events of PegIFN-α com-
pared with RBV therapy include anemia, thrombocy-
topenia, and leukopenia, which most frequently lead to
drug discontinuation or dose modifications. L-Carnitine
is a necessary nutrient factor in energy production and
has been proposed as a potential adjuvant treatment to
improve anemia, thrombocytopenia, and leukopenia.
A study comparing the PEGIFN-α plus RBV plus an
L-carnitine group versus the PEGIFN-α plus RBV group
observed a significant improvement in SVR for 50% vs
25% of patients[56]. This finding suggests that L-carnitine
supplementation may be useful in patients treated for
HCV. Other supplementations including erythropoietin,
zinc and probiotics have been assessed in clinical studies,
but the effects of those on SVR are still not clear.

FACTORS AFFECTING THE EFFICACY OF
HCV ANTIVIRAL THERAPY

The main factors influencing the efficacy of HCV anti-
viral treatments are divided into two categories: viral and
host-related. The viral category includes the HCV geno-
type, baseline viral load, and virological response during
treatment, and the host category includes age, gender,
race, drinking habits, obesity, degree of liver fibrosis,
and IL28B gene polymorphisms. In particular, IL28B
gene polymorphisms are associated with the SVR. With
approved DAAs on the market, more clinical treatment
choices have been provided. The efficient and reliable
prediction of the efficacy is essential to create individual
antivirus solutions, improve the efficacy, reduce the side
effects, and lower the treatment cost.

Viral factors
HCV genotype: Genotype plays an important role in
predicting the response to the SOC treatments and deter-
mining the appropriate antiviral treatment. The response
of patients with HCV genotype 1/4/5/6 infection is
worse than that of patients with genotype 2/3 infection.
DAAs are mainly used for the treatment of HCV geno-
type 1 infection. Although the effects of partial drugs on
non-type 1 infection have been evaluated, there have been
no sufficient data to clarify the relationship between the
genotype and the effect of DAAs. Short-term data from a
study on sofosbuvir indicated that the treatment with
sofosbuvir combined with the SOC regimen resulted in
a SVR12 of 91% in genotype 1 treatment-naïve patients
and 92% in patients with genotype 2/3. Another study
showed that sofosbuvir combined with RBV resulted in a
S VR rate of 84% in genotype 1 treatment-naïve patients
and 100% in patients with genotype 2/3[57]. Whether the
HCV genotype affects the efficacy of DAA treatment
remains to be confirmed by further studies.

Baseline viral load: Many studies have demonstrated
that, regardless of the HCV genotype, a low baseline vi-
ral load (before treatment, HCV RNA < 600000-800000
IU/mL) was an independent predictive factor of the
SVR[44,58,59]. In this range, the impact of the changes in
the HCV RNA concentration on the SVR was not linear;
when the HCV RNA was lower than 400000 IU/mL,
an increase in the amount of virus decreases the SVR
rate. However, an HCV RNA concentration higher than
400000 IU/mL results in a relatively stable SVR rate[51,60].
In 2011, the European guidelines for the prevention and
treatment of hepatitis C suggested that if the baseline
viral load was less than 400000-800000 IU/mL, the
course of treatment for genotype 1/4 naive patients who
received RVR can be shortened to 24 wk and that for
patients with genotype 2/3 may be shortened to 12-16
wk[52,61].

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Virological response during treatment: Using different patterns of response such as RVR, EVR, and delayed virological response (DVR: not having achieved RVR and EVR but testing negative for HCV RNA before the 24th wk) to predict the efficacy, determine the duration, and tailor the program can maximize benefits, rationalize the course of treatment, and minimize the recurrence rate. In the 2011 European guidelines\cite{51} for the prevention and treatment of hepatitis C, the following adjustments are made. For the genotype 1/4 patients, if the baseline viral load was low before treatment and RVR was acquired after treatment, the duration could be reduced to 24 wk. If the patient acquired DVR, the duration should be prolonged to 72 wk to reduce the recurrence rate. For the genotype 2/3 patients, if the baseline viral load was low and RVR was acquired, the duration could be shortened to 12-16 wk. For patients who did not acquire RVR and EVR or only acquired DVR or exhibit combined effects from other factors (such as obesity and insulin resistance), as long as the viral load was undetectable at the 24th wk, the duration could be extended to 48 or 72 wk. Regardless of the genotype, if the viral load decreased to less than 2 log IU/mL at the 12th wk and HCV RNA can still be detected at the 24th wk, the treatment could be discontinued. RGT principles are also applied to NS3 protease inhibitors. For HCV genotype 1 naive patients, using telaprevir or boceprevir combined with SOC and having acquired RVR and EVR, shortening the duration can be considered, but for patients with liver cirrhosis, a recommended treatment for 48 wk would be appropriate. The simprevir results show that, according to the RGT principle, the treatment duration in HCV genotype 1 naive patients can be shortened to 24 wk, but further research is needed to confirm this recommendation\cite{30}. The existing faldaprevir data show that extending the duration from 24 wk to 48 wk did not increase the SVR rate in HCV genotype 1 naive patients who achieved RVR and EVR, but for the previous treatment failure patients, a 48-wk course should be considered\cite{35,36}.

Host factors
Polymorphisms of the IL28B gene: In 2009, three genome-wide association studies (GWAS) found that single nucleotide polymorphisms (SNPs) in the $IL28B$ gene, located on chromosome 19, are associated with hepatitis C treatment efficacy\cite{62-64,65-67}. In patients with HCV type 1 infection, Ge et al\cite{33} found that rs12979860 (3 kilobases upstream of the $IL28B$ gene encoding the type III interferon IFN-λ3) showed a strong correlation with the treatment response. The SVR rate of SOC in CHC patients carrying the CC genotype was 2-3 times higher than that in patients not carrying the genotype. A Japanese study showed that rs8099917 was correlated with the HCV treatment response and was one of the most important predictors of non-response after the logistic regression analysis\cite{68}. The frequency difference in different populations with the rs12979860 CC genotype is very large, with East Asians having the highest frequency of the CC genotype\cite{69}, followed by Europeans, and with Africans having the lowest frequency\cite{70}. In a multivariate regression model, the $IL28B$ polymorphism was the best predictor of treatment response, being better than the ethnic background, baseline viral load, degree of liver fibrosis, fasting glucose level, BMI, and other predictors\cite{69,71-73}. Haf- fon et al\cite{71} analyzed the predictive values of rs12979860 and rs8099917 in 198 patients with HCV genotype 1 with respect to their response to treatment and showed that rs12979860 seemed to be sufficient for clinical decisions. EASL guidelines showed that $IL28B$ polymorphisms can be used to predict treatment response but have a low predictive value\cite{74}. In contrast, AASLD argues that for determining the treatment regimen (SOC regimen combined with or without DAA), the $IL28B$ polymorphism is a very strong predictor\cite{74,75}.

The predictive value of $IL28B$ polymorphisms is not only limited to SOC regimen but has also been demonstrated in a study from Japan in patients receiving triple therapy with telaprevir. The study showed that rs12979860 and rs8099917 were associated with SVR, and the univariate and multivariate analyses confirmed that rs8099917 can be used as an independent predictor of the SVR\cite{74,76}. Similar results were also found in other studies on the SOC treatments combined with DAA\cite{77-79}. An IFN-free study of merci- tabine as a monotherapy or in combination with danoprevir showed that the rs12979860 CC genotype was related to faster and earlier viral decline\cite{76}.

Thus, the $IL28B$ gene has a better predictive value with respect to not only the SOC but also DAA. However, further research is still needed to confirm these observations.

Hepatic steatosis and other negative predictors: The value of steatosis as a negative predictor of response to anti-HCV therapy was confirmed in two large clinical trials. In one study, 574 HCV patients treated with the SOC were evaluated, and the results showed that the presence of steatosis reduces the likelihood of achieving EVR and SVR in genotype-1 infected patients\cite{78}. In another study, 231 HCV patients treated with the SOC were evaluated\cite{80}. The results showed that steatosis negatively affected SVR in HCV genotype non-3-infected patients. In the last year, new data showing that steatosis is also an independent predictor of relapse in genotype 3 have been published\cite{81}. Steatosis has been associated with significantly higher rates of relapse, irrespective of viral load, in patients infected with HCV genotype 3 who had a rapid virological response (RVR)\cite{78,82}. Several studies\cite{83,84} have shown that RVR consistently remains an important determinant of SVR in patients with HCV genotype 2 or 3. Recent studies have confirmed that RVR is a good indicator for SVR in genotype 2, but not in genotype 3, in which steatosis is a predictor of relapse. This suggests that the underlying pathogenic mechanisms of steatosis differ between genotype 3 and other genotypes and may influence response to IFN-based therapy. These data sug-
gest that new therapeutic strategies are necessary for this subgroup of HCV genotype 3[85,86].

Other adverse predictive factors affecting the efficacy of HCV treatment include liver cirrhosis[50], age ≥ 40 years old[80], insulin resistance[81,82] and metabolic syndrome[83,84]. In patients with these factors, either the treatment duration may need to be extended or the dose may need to be increased.

CONCLUSION

PegIFN-α combined with RBV is currently the most classic and widely used standard treatment; however, its limited efficacy and significant side effects, as well as the absence of an HCV vaccine, promoted the development of new drugs. In recent years, the development of HCV antiviral drugs has progressed. Two HCV NS3 protease inhibitors, telaprevir and boceprevir, were approved by the United States FDA in 2011, and their combined treatment with the SOC not only significantly improved the SVR rate in HCV naïve patients but also showed good efficacy in patients with previous treatment failure. Many other HCV NS3 protease inhibitors, NS5A inhibitors, and NS5B RdRp inhibitors are in the final stage of clinical trials and are likely to soon be approved as anti-HCV drugs. DAAs have shown a trend toward a gradual replacement of the SOC scheme. Although the efficacy of DAAs is significantly improved, the incidence of treatment-related side effects appears to be high, and because of the direct-acting antiviral effect, resistance mutations appear to be more likely to appear. Therefore, the implementation of personalized treatment approaches is very important. The application of many HCV antiviral drugs provides clinicians with more effective treatment choices for CHC. Host genetic factors guide individualized treatment strategies and aid in determining the best treatment plan for each patient. Polymorphisms in the IL28B gene have been used in clinical practice to help determine anti-HCV treatment strategies. Genetic markers need further verification, which can be performed in the preclinical testing stage. At the same time, accurately predicting the success of treatment and the progression of the disease will enhance the treatment compliance of patients, which will aid in maximizing the treatment effect.

Although DAAs show good potential, it is difficult to completely overcome the associated drug toxicity and occurrence of drug resistance; thus, not all patients can be cured by antiviral therapy. Therefore, determining how to prevent infection with HCV is an important research direction. Over the years, HCV vaccine development strategies are mostly based on the viral genome, unable to overcome HCV high variability, and starting from the human genome to explore other ways to prevent HCV infection may open up a new era in infection prevention.

REFERENCES

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5: 558-567.
2. Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? J Hepatol 2012; 56 Suppl 1: 556-565. [PMID: 22300466 DOI: 10.1016/S0168-8278(12)60077-5].
3. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013; 59: 169-177. [PMID: 23542809 DOI: 10.1016/j.jhep.2013.03.018].
4. Gembtskii EV, Glazunov AV, Zhilaev EV, Proskurina TV. Extrahepatic syndromes (vascular manifestations) in patients HCV infection. Klin Med (Mosk) 1995; 73: 51-53. [PMID: 8961784].
5. Buskila D. Hepatitis C-associated rheumatic disorders. Rheum Dis Clin North Am 2009; 35: 111-123. [PMID: 19481000 DOI: 10.1016/j.rdc.2009.03.005].
6. Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Costanzo GG, Lanza AG, Picciotto FP, Marino-Marsilia G, Fontanella L, Leonadro G. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology 2010; 138: 116-122. [PMID: 19852964 DOI: 10.1053/j.gastro.2010.09.005].
7. Kamal SM, Ahmed A, Mahmoud S, Nabeeg L, El Gohary I, Obadan I, Hafez T, Ghoraiba D, Aziz AA, Metaeai M. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int 2011; 31: 401-411. [PMID: 21281434 DOI: 10.1111/j.1478-3231.2010.02435.x].
8. Rumi MG, Aghemo A, Prati GM, D’Ambrosio R, Donato MF, Soffredini R, Del Ninno E, Russo A, Colombo M. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology 2010; 138: 108-117. [PMID: 19766645 DOI: 10.1053/j.gastro.2009.08.071].
9. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Kouri K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009; 361: 580-593. [PMID: 19625712 DOI: 10.1056/NEJMoa080810].
10. Manns M, Zeuzem S, Sood A, Lurie Y, Cornberg M, Klinker H, Buggisch P, Rösse M, Hinrichsen H, Merican I, Ilan Y, Mauß S, Abu-Mouch S, Horban A, Müller TH, Welsch C, Chen R, Faraqui R, Pedicone LD, Wedemeyer H. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol 2011; 55: 554-563. [PMID: 21257227 DOI: 10.1016/j.jhep.2010.12.024].
11. Krawitt EL, Gordon SR, Grace ND, Ashikaga T, Ray MA, Palmer M, Yarce JC, Moskwitz S. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol 2006; 101: 1268-1273. [PMID: 16771948 DOI: 10.1111/j.1572-0241.2006.00614.x].
12. Sood A, Midha V, Hissar S, Kumar M, Sunetha PV, Bansal M, Sood N, Sakhuja P, Sarin SK. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol 2008; 23: 203-207. [PMID: 17645472 DOI: 10.1111/j.1440-1746.2007.05075.x].
13. Hadziyannis SJ, Seite H, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346-355.
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J Hepatol 2012; 56: S5-S6 [DOI: 10.1016/S0168-8278(12)60024-5]

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, McLennan M, Muir AJ, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kaufmann RS, George S, Wright CI, Poordad F. Response-guided telaprevir combination treatment for hepatitis C virus infection. J Hepatol 2010; 53: 790-798 [DOI: 10.1016/j.jhep.2010.06.062]

Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, McLennan M, Muir AJ, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kaufmann RS, George S, Wright CI, Poordad F. Response-guided telaprevir combination treatment for hepatitis C virus infection. J Hepatol 2010; 53: 790-798 [DOI: 10.1016/j.jhep.2010.06.062]

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Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, McLennan M, Muir AJ, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kaufmann RS, George S, Wright CI, Poordad F. Response-guided telaprevir combination treatment for hepatitis C virus infection. J Hepatol 2010; 53: 790-798 [DOI: 10.1016/j.jhep.2010.06.062]
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References

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Angus PW, Ritchie B, Lu XY, Ipe D, Lopatin U, Germer S, Iglesias VA, Elston R, Smith PF, Shulman NS. Effect of IL28B genotype on early viral kinetics during interferon-free treatment of patients with chronic hepatitis C. *Gastroenterology* 2012; 142: 790-795 [PMID: 22248659 DOI: 10.1053/j.gastro.2011.12.057]

Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vällée M, Heaton S, Conrad A, Pockros PJ, McHutchison JG. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. *J Hepatol* 2004; 40: 484-490 [PMID: 15123364 DOI: 10.1016/j.jhep.2003.11.004]

Westin J, Lagging M, Dhillon AP, Norkrans G, Romero AI, Pawlotsky JM, Zeeuwen S, Schalm SW, Verheij-Hart E, Negro F, Missale G, Neumann AU, Hellstrand K. Impact of hepatic steatosis on viral kinetics and treatment outcome during antiviral treatment of chronic HCV infection. *J Viral Hepat* 2007; 14: 29-35 [PMID: 17212641 DOI: 10.1111/j.1365-2893.2006.00777.x]

Shah SR, Patel K, Marcellin P, Foster GR, Manns M, Kottilil S, Healey L, Pulkstenis E, Subramanian GM, McHutchison JG, Sulkowski MS, Zeeuwen S, Nelson DR. Steatosis is an independent predictor of relapse following rapid virologic response in patients with HCV genotype 3. *Clin Gastroenterol Hepatol* 2011; 9: 688-693 [PMID: 21640198 DOI: 10.1016/j.cgh.2011.04.029]

Restivo L, Zampino R, Guerrera B, Ruggiero L, Adinolfi LE. Steatosis is the predictor of relapse in HCV genotype 3- but not 2-infected patients treated with 12 weeks of pegylated interferon-α-2a plus ribavirin and RVR. *J Viral Hepat* 2012; 19: 346-352 [PMID: 22497814 DOI: 10.1111/j.1365-2893.2011.01555.x]

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