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Review Article

Interferon-Based Therapy for Chronic Hepatitis C : Present and Future Perspectives

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Abstract

Pegylated interferon α (peginterferon α) plus ribavirin is the present mainstay of treatment for patients with chronic HCV infection. When peginterferon α plus ribavirin is administered for the standard duration, a sustained virological response is achieved in around 50% of patients infected with HCV genotype 1 and around 80% of patients infected with HCV genotype 2 or 3. Data now suggest that treatment duration can be shortened or lengthened depending on baseline viral load and/or early on-treatment viral kinetics, offering the prospect of individualizing therapy further to improve response or to prevent treatment from being unnecessarily extended. Further efforts to optimize therapy are likely to involve the use of new anti-HCV agents, several of which are currently in the early stages of development. These agents include HCV protease inhibitors (particularly those against NS3-4A protease), HCV polymerase inhibitors (including both nucleoside and non-nucleoside analogs) and cyclophilin inhibitors. These compounds will be used, at least initially, in combination with peginterferon α plus ribavirin, extending the pivotal role of interferon-based therapy in the management of chronic hepatitis C.

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Introduction

Since the first reported use of interferon **α** (IFN- **α**) for the treatment of chronic hepatitis C more than 20 years ago,[1] IFN-based therapy has become the cornerstone of treatment for this disease. Pegylated IFN- **α** (peginterferon **α**) which was developed to ensure sustained exposure with once-weekly dosing, offers improved convenience, a better adverse effect profile and, above all, superior clinical efficacy compared with IFN-α. For these reasons peginterferon α has replaced conventional IFN-α for the treatment of chronic hepatitis C. Today, the combination of peginterferon α 2a or peg-interferon α 2b plus ribavirin (RBV) is the standard of care for chronic hepatitis C[2-5].

The primary goal of treatment for chronic HCV infection is a sustained virological response (SVR), which is defined clinically as HCV RNA levels undetectable with a sensitive molecular assay 24 weeks after cessation of therapy[2]. Patients who achieve an SVR have a greater than 95% chance of still being virus-free 5 years later[6]. This end point is associated with regression of fibrosis, decreased incidence of hepatocellular carcinoma, and overall reduced morbidity and mortality[7].

Presently, around 50% of patients infected with HCV genotype 1, 80-93% of those infected with HCV genotype 2 and 66-80% of those infected with HCV genotype 3 achieve an SVR with peginterferon plus RBV treatment, which is a

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major improvement compared with the SVR associated with conventional IFN-α therapy[8]. A substantial proportion of patients, however, do not have an optimum response to current treatment regimens. Individualization of therapy offers the possibility of tailoring treatment to particular patients and selecting the treatment duration that ensures the best chance of achieving an SVR while preventing over-treatment. Key to this individualization strategy is an understanding of the kinetics of viral response to therapy, aspects of which are discussed in this Review.

The development of new anti-HCV agents might also help improve treatment outcome. The study of viral kinetics offers a means of comparing different treatment regimens and assessing response to new agents, a number of which have shown promise in preliminary studies. Although novel anti-HCV drugs are still in the early stages of development, it is hoped that these agents might not just increase SVR rates, but also reduce treatment duration and improve tolerability. This Review describes the Present standard of care as well as future perspectives in the treatment of hepatitis C.

Mechanism of Action

IFN-α has potent antiviral properties. Treatment with IFN-α induces the expression of a range of antiviral effector proteins, of which the best known include 2',5'-oligoadenylate synthetase, double-stranded RNA-activated protein kinase, and the myxovirus proteins.[9] In addition to its direct antiviral properties, IFN-α has immuno-modulatory properties that might contribute to its antiviral efficacy by activating cells and molecules involved in the host antiviral response. Although the exact mechanisms contributing to the clinical efficacy of IFN-α are not completely understood, several indirect antiviral functions have been demonstrated. For example, IFN-α stimulates the effector function of natural killer cells, cytotoxic T lymphocytes and macrophages, up-regulates the expression of major histocompatibility complex class I and class II molecules, induces immunoglobulin synthesis by B cells, and stimulates the proliferation of memory T cells[9].

The overall pattern of viral response to IFN-based therapy can be used to determine the likelihood of treatment success and guide treatment duration in patients with chronic hepatitis C. The primary goal of treatment for chronic HCV infection is an SVR. Patients who fail to achieve an early virological response (EVR), which is defined as either an undetectable level of HCV RNA or a drop in HCV RNA levels of at least $2\log_{10}$ IU/ml after 12 weeks of therapy, are highly unlikely to go on to achieve an SVR —the negative predictive value in this setting is around 97%.[10] These findings form the basis of the week 12 stopping rule for HCV genotype 1 infected patients, as discussed below[10]. Testing for rapid virological response (RVR), which is defined as an undetectable level of HCV RNA (<50 IU/ml) at 4 weeks of treatment, has been shown to offer further prospects for the individualization of therapy according to treatment-related viral kinetics[11].

Current Guidelines for the Treatment of Patients with HCV

HCV genotype and treatment duration

The main baseline predictor of response to therapy is HCV genotype, and genotype is consequently the primary determinant of treatment duration and response monitoring procedures in present treatment recommendations[2-5]. Patients infected with HCV genotype 1 or 4 should receive 48 weeks of peginterferon α plus RBV, while 24 weeks of treatment is recommended for patients with an HCV genotype 2 or 3 infection.

Data for patients infected with HCV genotypes other than 1-4 were limited or lacking when present treatment guidelines were developed; thus, it is recommended that such individuals are treated in the same way as patients with HCV genotype 1 infections. Data now indicate that this is an appropriate approach; for example, patients infected with HCV genotype 6 have a higher rate of SVR with 48 weeks of treatment than with 24 weeks[12]. The response to treatment in patients infected with HCV genotype 4 seems to be at an intermediate level compared with that of patients infected with HCV genotype 1 or 3[13].

The indicated doses for the two approved peginterferons, peginterferon α 2a (180 μg once weekly) and peginterferon α 2b (1.5 μg/kg once weekly), are independent of HCV genotype, but there are different recommendations for RBV dose depending on genotype and body weight[14,15]. For patients with an HCV genotype 1 or 4 infection, weight-based RBV doses of 800-1,200 mg per day (l,400mg per day for patients who weigh > 105 kg receiving peginterferon α 2b) are recommended. For patients with an HCV genotype 2 or 3 infection the recommended dose of RBV is 800 mg per day, and there is no additional benefit associated with higher doses (at least for the 24-week standard treatment duration).

On-treatment response and treatment duration

Present recommendations for patients infected with HCV genotype 1 or 4 include the week 12 stopping rule. This rule states that if a patient fails to achieve an EVR, consideration should be given to stopping treatment as achieving an SVR is unlikely[10]. Almost all patients with an HCV genotype 2 or 3 infection have an EVR; therefore, recommendations do not suggest measuring HCV RNA at week 12 in these patients but simply treating them for 24 weeks. Further individualization of therapy- the role of viral response.

There is increasing evidence to suggest that current dosing regimens for peginterferon α could potentially result in the over-treatment of some patients who respond well to treatment and are more likely to achieve an SVR or, conversely, the under-treatment of those patients who respond less well[16]. Evidence is growing to support the taking of additional measurements of viral response to facilitate individualization of therapy for such patients.

Rapid virological response and shorter treatment duration

The presence of an RVR is the strongest inde-pendent positive predictor of the likelihood of achieving an SVR for all HCV genotypes[17]. The rapid response seen in some patients has given rise to the question as to whether such individuals might respond equally well, in terms of SVR, to a shorter treatment duration.

Early studies using conventional IFN-α, such as the study by Poynard and co-workers, indicated that patients infected with HCV genotype 1 who had low pretreatment viral loads (≤ 2,000,000 copies/ml;~800,000 lU/ml) could be treated for 24 weeks without compromising SVR rates[18]. In a study by Zeuzem and colleagues, response rates at the end of treatment with peginterferon α 2b plus RBV were similar among HCV genotype 1 infected patients with low baseline viral load (≤ 600,000 IU/ml); however, overall SVR rates achieved with 24-week treatment were significantly lower than those observed in historical controls treated for 48 weeks, owing to a high virologic relapse rate in patients treated for 24 weeks[19].

The study by Zeuzem *et al.* found that a subset of HCV genotype 1 infected patients with baseline HCV RNA levels below 600,000 lU/ml plus undetectable serum levels of HCV RNA at week 4 of treatment (RVR) had a similar rate of SVR after 24 weeks of therapy to the historical control group treated for 48 weeks (89% and 85%, respectively) [19]. The importance of an RVR in predicting an SVR was confirmed in a retrospective analysis, which showed that HCV genotype 1 infected patients who achieved an RVR when treated with a standard regimen of peginterferon α 2a plus RBV (around 24% of patients) were highly likely to achieve an SVR (89% vs 19% for patients with and without an RVR, respectively)[20]. Baseline viral load was shown to be predictive of an RVR, and patients with baseline HCV RNA levels of 800,000 lU/ml or lower were more likely to achieve an RVR than were those with baseline HCV RNA levels greater than 800,000 IU/ml[20].

Additional evidence supporting the shortening of treatment duration to 24 weeks in patients with low viral loads and an RVR has accumulated not only from studies in patients infected with HCV genotype 1, but also from those in patients infected with HCV genotype 4[21,22]. As a result, both peginterferon α 2a and peginterferon α 2b have been approved in the European Union for a shortened treatment duration of 24 weeks in HCV genotype 1 patients with a low viral load (defined

as <800,000 lU/ml for peginterferon α2a and <600,000 IU/ml for peginterferon α2b) and an RVR[14,15].

For patients infected with HCV genotype 2 or 3, the results of several studies have indicated that individuals who achieve an RVR could be candidates for treatment duration of less than 24 weeks[23-26]. Indeed, a number of studies have demonstrated comparable SVR rates with 16 weeks and 24 weeks of treatment in patients who achieve an RVR[23-26]. Among patients who had an RVR in the large-scale, randomized, multinational ACCELERATE study, however, the SVR rate was significantly higher in the 24-week treatment group than in the 16-week treatment group (85% vs 79%; P<0.001), although patients who achieved an RVR were more likely to achieve an SVR overall.[27] The difference in SVR rates reflects a significantly higher relapse rate in the 16-week treatment group than in the 24-week treatment group (31% vs 18%; P< 0.001). This difference was seen in both patients infected with HCV genotype 2 and those infected with genotype 3[27].

Slow virological response and longer treatment duration

There is increasing evidence to support extending the duration of treatment beyond 48 weeks in patients with an HCV genotype 1 infection who have a slow virological response (i.e. HCV RNA levels >50 lU/ml at week 12, but undetectable [<50 IU/ml] at week 24)[29-32]. In a study of HCV genotype 1 infected patients treated peginterferon α2a (180 μg once weekly) plus RBV (800 mg per day), extending treatment duration to 72 weeks did not increase the SVR rate in the intention to treat population[29]. Patients who still had detectable levels of HCV RNA ($\geq$50 IU/ml) at week 12 according to the results of a sensitive molecular test, however, had a significantly higher SVR rate when treated for 72 week than for 48 weeks (29% vs 17%; P=0.04), with the greatest benefit observed in patients who had HCV RNA levels below 6,000 lU/ml at week12[29]. These findings were subsequently confirmed in a study in HCV genotype 1 infected patients who met the criteria for an EVR and had detectable levels of HCV RNA at week 12, but had undetectable levels at week 24. In this trial, 72 weeks of treatment with pegylated interferon α2b plus weight-based dosing of RBV resulted in a better SVR rate than the same treatment for 48 weeks (39%vsl8%)[31].

In HCV genotype 1 infected patients who do not achieve an RVR, extending treatment to 72 weeks also significantly increases the SVR rate compared with 48 weeks of therapy; for example, Sanchez-Tapias *et al*. reported SVR rates of 44% and 28% with 72 weeks and 48 weeks of treatment, respectively (P = 0.003)[30]. In an analysis of three European studies,[29,30,33] 72 weeks of treatment was found to consistently improve the rates of SVR in patients who had a decline in HCV RNA levels of more than $2\log_{10}$ IU/ml but still had detectable levels of HCV RNA at week 12 of treatment[34]. Taken together, the available data show that longer duration of therapy improves rates of SVR in `slow' virological responders infected with genotype 1.

HCV genotype 2 or 3 infected patients who have a high baseline viral load and/or do not achieve an RVR have low SVR rats after peginterferon α plus RBV therapy[10,25,27,35]. High baseline HCV RNA levels (>600,000 IU/ml) are associated with a high rate of virological relapse (23%) in HCV genotype 3 infected patients,[35] and data from the ACCELERATE study showed that patients infected with HCV genotype 2 or 3 who did not achieve an RVR had only a 49% probability of achieving an SVR[27]. These data raise the question of whether such patients might benefit from more-intensive treatment than is currently used. In a retrospective analysis of data from two large clinical trials, most HCV genotype 2 or 3 infected patients were found to have achieved an RVR; however, among patients without an RVR, the SVR rate was higher and relapse rate lower for those receiving 48-week treatment with higher doses of RBV (1,000-1,200 mg per day) than for those receiving 24-week treatment with a lower dose of RBV (800 mg per day)[36,37]. These results need to be confirmed in a prospective controlled study, but it is possible that patients with an HCV genotype 2 or 3 infection who do not achieve an RVR could benefit from longer treatment with peginterferon α and higher doses of RBV(>800 mg per day).

A final consideration concerns the assumption that HCV genotype 2 and genotype 3 infections require a similar duration of treatment. Evidence now indicates that this might not be the case. HCV genotype 2 infected patients seem to respond better to therapy and have consistently higher SVR rates than do HCV genotype 3 infected patients, with an overall SVR rate of 80-93% compared with 66-80%, respectively, after treatment for up to 24 weeks[23,25,28]. These differences are also seen following the same duration of treatment in patients who achieved an RVR (SVR rate 87-95% for genotype 2 vs 76-89% for genotype 3)[23,25,28]. These findings indicate that separate management algorithms, possibly with a longer treatment duration for HCV genotype 3 infected patients, could be appropriate, and further studies are required to confirm whether this is the case.

Re-treatment of patients

The management of patients with chronic hepatitis C who relapse after treatment (i.e. those who achieve an end of treatment virological response but not an SVR) or who fail to respond to current standard IFN-based therapy presents a particular problem. In patients who relapse after a first treatment course of IFN-α alone, combination therapy with IFN-α plus RBV has been shown to lead to substantially higher SVR rates than an additional course of IFN-α monotherapy[35]. In the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, 18% of patients who did not respond to or had relapsed after treatment with conventional IFN-α or conventional IFN-α plus RBV had an SVR in response to re-treatment with 48 weeks of peginterferon α 2a plus RBV[38] Factors associated with an SVR included previous treatment with IFN-α monotherapy, infection with HCV genotype 2 or 3, a low serum aspartate aminotransferase to serum alanine aminotransferase (ALT) ratio, and the absence of cirrhosis. Similar findings were reported in the Evaluation of Peglntron in Control of Hepatitis C Cirrhosis (EPIC-3) trial, with 23% of patients who did not respond or who had relapsed after previous IFN-based treatment achieving an SVR following re-treatment with peginterferon α 2b plus RBV[39].

Patients who relapse after treatment with conventional IFN-based regimens often respond to re-treatment with peginterferon α plus RBV, with SVR rates of 41-59% being reported[35]. Pegjnterferon α plus RBV re-treatment should, therefore, be considered for all patients who have previously responded to a conventional IFN-based regimen and subsequently relapsed.

Re-treatment of non-responders to IFN-α is generally associated with poor SVR rates, especially in HCV genotype 1 infected patients or patients with cirrhosis[35]. Evidence now suggests, however, that prolonged re-treatment of non-responders significantly improves SVR rates. In the Re-treatment with Pegasys in Patients Not Responding to Peg-Intron Therapy (REPEAT) study, 72 weeks of treatment produced an overall SVR rate of 16% compared with 8% after 48 weeks of treatment ($P = 0.006$)[40]. In this study, patients who had undetectable levels of HCV RNA after 12 weeks of treatment were more likely to achieve an SVR after 72 weeks treatment than were those who had detectable levels of HCV RNA (57% vs 4%). These findings indicate that duration of therapy could be pivotal to improving the outcome in nonresponders to IFN-α.

Another potential strategy to achieve a response in patients who are unresponsive to the standard of care is to use increased doses of RBV, as described by Lindahl *et al.* in a small study of previously untreated patients.[41] In their study, the authors used high doses of RBV (1,600-3,600 mg per day), tailored to each patient according to an individualized schedule. Although *9* out of 10 patients achieved an SVR, suggesting that this approach is feasible, the use of such high RBV doses was associated with more-frequent and more-serious adverse effects such as anemia.

Even in patients who do not achieve an SVR, IFN-based regimens can reduce hepatic inflammation. Given that progression of fibrosis to cirrhosis is a function of hepatic inflammation, it has been suggested that IFN-based maintenance therapy might slow disease progression[42,43]. In addition, although some patients are classified as virological relapsers and/or nonresponders, they might have a biochemical response to treatment (i.e. reduction

or normalization of ALT levels). Results from the NIH-sponsored HALT-C trial showed that peginterferon α 2a maintenance therapy improved ALT level, HCV viral load, and necroinflammation[42]. Despite these results, however, there was no long-term effect on the rate of disease progression[42]. In a similar study that compared the effects of low-dose peginterferon α 2b with those of low-dose colchicine (Colchicine Versus PEG-Intron Long Term [COPILOT] study), the rate of bleeding from esophageal varices observed in patients treated with peginterferon α 2b for up to 4 years was lower than that in patients who received colchicine[43].

Guidelines recommend that decisions regarding re-treatment should include consideration of the severity of the underlying liver disease, adherence and/or compliance, tolerance issues, the previous therapy and type of response to it, viral genotype, and other predictive factors for response[2].

Future Therapies

Despite the undoubted benefits brought to the treatment of chronic hepatitis C by the introduction of peginterferon α, there remains an ongoing need for improved treatment strategies and for new therapeutic agents to increase response rates, particularly in patients whose characteristics make them difficult to cure. Although novel IFN-based products continue to be developed, interest is focusing on different classes of anti-HCV drugs. Several HCV-specific inhibitors are under investigation in preclinical and clinical trials, and it is anticipated that these agents will improve treatment options for patients with chronic hepatitis C. To date, the most promising treatment targets are the HCV protease NS3-4A, which is responsible for protein maturation during viral reproduction, and the RNA-dependent HCV polymerase NS5B. Development of new anti-HCV drugs is, of course, not without its challenges, and several polymerase inhibitors have already been discontinued from development primarily on the basis of unacceptable levels of toxicity or lack of adequate efficacy. Those new anti-HCV drugs that have performed well at least in proof of concept trials or seem to be the most promising are discussed below.

Protease Inhibitors

The first potent and specific inhibitor of NS3-4A serine protease to be tested in a randomized, placebo-controlled pilot study in patients with chronic hepatitis C was ciluprevir (BILN 2061)[44]. In previously untreated patients infected with HCV genotype 1, treatment with ciluprevir for 2 days resulted in viral RNA reductions of 2-3 $\log_{10}$ copies/ml in most patients, thus providing proof of concept that inhibitors of HCV NS3-4A protease are a therapeutic option for patients with chronic hepatitis C. Further clinical development of ciluprevir has been suspended, however, following reports of cardiotoxicity in animal studies[44]. The NS3-4A protease inhibitors telaprevir[45] and boceprevir[46] have since been shown to reduce serum HCV RNA levels when used alone and to produce additive reductions in serum HCV RNA levels when administered with peginterferon α plus RBV.

Telaprevir

In a trial by Reesink and co-workers, telaprevir monotherapy for 2 weeks was associated with a median reduction in HCV RNA levels of more than $4\log_{10}$ IU/ml in patients with chronic hepatitis C who had a genotype 1 infection[45]. When used as monotherapy, however, telaprevir has a low barrier against the development of genetic resistance by HCV, which is a potential problem for antiviral agents given the high rate and error-prone nature of HCV replication[47].

Triple therapy with telaprevir, peginterferon α 2a and RBV not only improves antiviral activity, but also significantly reduces the incidence of resistance[48,49]. Preliminary data from two phase II trials in HCV genotype 1 infected patients (PROVE 1 and PROVE 2) demonstrated that triple therapy significantly increased the incidence of RVR at week 4 and complete EVR at week 12 compared with peginterferon α 2a plus RBV[48,49]. Final data presented during the 2008 annual meeting of the European Association for the Study of the Liver showed SVR rates as high as 61% (PROVE 1) and 68% (PROVE 2) in HCV genotype 1 infected patients treated for 12 weeks with the triple therapy regimen followed by 12 weeks of standard-dose peginterferon α 2a plus

RBV[50,51]. The total incidence of adverse events in patients treated with telaprevir, peginterferon α 2a and RBV was similar to that in the control group; however, discontinuation because of adverse events was more frequent in the triple therapy arm than in the control arm (9% vs 3%). Gastrointestinal events, rashes (in several cases severe) and anemia were more common in the triple therapy arm than in the standard combination treatment arm.

Boceprevir

Boceprevir in combination with peginterferon α 2b has been compared with either agent alone in patients with an HCV genotype 1 infection who were previous nonresponders to peg-interferon-based therapy[46]. In this three-period crossover trial, patients were randomly allocated to receive, in a random sequence, boceprevir (200 mg or 400 mg every 8h) as monotherapy for 7 days, Peginterferon α 2b as monotherapy for 14 days and boceprevir plus peginterferon α 2b combination therapy for 14 days, with a 3-week washout between treatments. Mean maximum changes in HCV RNA levels were highest when patients received combination therapy compared with monotherapy[46]. A sensitive clonal analysis of HCV quasispecies present in patients treated with boceprevir has revealed that there is selection of different variants of NS3 protease, with different resistance levels to NS3 inhibitors and resistance frequencies proportional to HCV RNA levels[52].

Boceprevir has also been evaluated in combination with peginterferon α 2b with and without RBV, in one instance for 24 weeks or 48 weeks in a phase II dose-ranging study in patients with an HCV genotype 1 infection who were nonresponders to previous treatment with peginterferon α plus RBV,[53] and also in the phase II Serine Protease Inhibitor Therapy-1 (SPRINT-1) study in treatment-naive HCV genotype 1 infected patients[54]. The virological response rates in previous nonresponders were generally low in the dose-ranging study[53]. In the SPRINT study, however, 55% and 57% of previously untreated patients achieved undetectable levels of HCV RNA 12 weeks after the end of 24 weeks of triple therapy with peginterferon α 2b, RBV and boceprevir without and with a 4-week lead phase consisting of peginterferon α 2b plus RBV alone, respectively[54].

Polymerase Inhibitors

The polymerase inhibitor class of antiviral agents includes nucleoside analogs and non-nucleoside analogs. Nucleoside analogs target the catalytic site of HCV polymerase and inhibit the initiation of HCV RNA transcription and the elongation of the nascent RNA chain. By contrast, non-nucleoside analogs bind to a number of discrete sites on HCV polymerase. Several inhibitors of HCV polymerase have been evaluated in clinical trials, including the nucleoside inhibitors valopicitabine, R1626 and R7128 and the non-nucleoside inhibitors GS-9190, HCV-796 andVCH-759.

Nucleoside analog polymerase inhibitors

In a trial by Zhou and co-workers, patients infected with HCV genotype 1 who were non-responders to IFN-based antiviral treatment showed a mean reduction in HCV RNA levels of 0.15-1.21 $\log_{10}$IU/ml after 14 days of treatment with 50-800 mg/day valopicitabine[55]. When valopicitabine was administered in combination with peginterferon α 2b, a decline in HCV RNA levels of 3.75-4.41 $\log_{10}$ IU/ml was reported after 36 weeks of treatment[56]. Significant gastrointestinal adverse effects were observed in particular at doses above 200 mg/day. Thus, on the basis of the overall risk-benefit profile observed in clinical testing, the clinical development of valopicitabine for the treatment of hepatitis C has been placed on hold.

R1626 is an oral pro-drug of the potent and selective nucleoside analog polymerase inhibitor R1479[57]. In a multiple-dose, dose-ascending, phase I study in previously untreated patients with an HCV genotype 1 infection, 14 days of treatment with twice daily doses of 1,500 mg, 3,000 mg or 4,500 mg R1626 resulted in mean viral load reductions of 1.2 $\log_{10}$ lU/ml, 2.6$\log_{10}$ IU/ml and 3.7$\log_{10}$IU/ml, respectively[57]. A phase II trial in HCV genotype 1 infected patients showed that triple therapy with R1626,

peginterferon α 2a and RBV produces a synergistic effect, achieving a more-profound reduction in HCV RNA levels at week 4 of treatment than peginterferon α 2a plus RBV[58]. A total of 81% of patients treated with the triple therapy regimen had undetectable levels of HCV RNA (<50IU/ml) at week 4 compared with 5% of those treated with the standard regimen of peginterferon α 2a plus RBV. Adverse events reported in patients receiving R1626 were mild to moderate, although grade 4 neutropenia was observed in 39 patients (78%) receiving triple therapy and was the main reason for dose reductions[58]. So far there is no evidence of resistance to R1626 in clinical isolates taken from patients treated with the drug, implying that R1626 has a high genetic barrier to the development of resistance by HCV[59].

R7128 is a pro-drug of PSI-6130, which is an oral cytidine nucleoside analog. No toxicity has been observed with R7128 in preclinical studies in various human cell lines, including liver cells, bone marrow cells, and white blood cells[60]. It appears that R7128 is more active at lower concentrations than other such compounds in development[60]. In preclinical assays, PSI-6130 was found to have additive effects on the activity of IFN-α alone[60]. A phase I trial of R7128 in combination with peginterferon α 2a plus RBV is currently underway in treatment-naive patients with an HCV genotype 1 infection[61]. Preliminary results showed potent antiviral activity in patients treated with R7128 1,500 mg per day, peginterferon α 2a and RBV, with 17 (85%) of 20 patients achieving an RVR[61].

Non-nucleoside polymerase inhibitors

HCV-796 is a non-nucleoside inhibitor of the RNA polymerase NS5B. This inhibitor has demonstrated potent antiviral activity, with Villano et al recording a maximum antiviral effect after 4 days of treatment that resulted in a mean reduction in HCV RNA levels of 1.4 $\log_{10}$ lU/ml; however, an increase in viral load thereafter indicated that resistance might be an issue[62]. In a study of treatment-naive patients with chronic hepatitis C, the combination of HCV-796 and peginterferon α 2b resulted in a mean reduction in viral load of 3.3-3.5$\log_{10}$ IU/ml after 14 days of treatment compared with 1.6$\log_{10}$ IU/ml with peginterferon α 2b alone; antiviral activity was greatest in patients who had a non-genotype 1 infection[62]. Safety issues concerning clinically significant elevations of liver enzyme levels in phase II trials have, however, led to the discontinuation of the phase II program.

GS-9190 is another non-nucleoside polymerase inhibitor that has been investigated in a phase I clinical trial in treatment-naive patients with an HCV genotype 1 infection[63]. Following single-dose exposure (40-480 mg), a maximum antiviral effect was observed at 24 h, with median declines in HCV RNA levels of 0.46-1.49 $\log_{10}$ IU/ml across doses[63]. An instance of possible QT elongation was observed during a multi-dose exposure trial and a specific study of the effect of GS-9190 on QT interval in healthy volunteers is underway.

A proof of concept study has also been completed for VCH-759 in treatment-naive HCV genotype 1 infected patients[64]. Declines in HCV RNA level of 21og$_{10}$ IU/ml or more were achieved with 800 mg three times daily over a 10-day dosing period. As has been found with other non-nucleoside polymerase inhibitors, however, selection of mutants conferring drug resistance has been observed in patients treated withVCH-759[65].

Other inhibitors of HCV

Other inhibitors of HCV in early clinical development include the cyclophilin inhibitor Debio-025,[66] celgosivir (an oral prodrug of castanospermine that inhibits the enzyme gluco-sidase in hte host),[67] and nitazoxanide (an oral prodrug of the thiazolide tizoxanide that inhibits HCV replication by an unknown mechanism of action)[68.]

Combination therapy with direct antivirals

The high error rate of the RNA polymerase for HCV means that HCV variants are continuously produced during replication, and infected cells thus have the potential to produce multiple drug-resistant mutants over time. The emergence of such mutants could limit the success of HCV-

specific antiviral compounds and is, therefore, a highly relevant clinical issue. Experience from the HIV field indicates that combining antiviral agents not only has the potential to improve efficacy, but also, if compounds with different resistance profiles are used, to reduce the risk of developing treatment-resistant mutations of HCV. In vitro studies suggest that combined treatment with a protease inhibitor and a polymerase inhibitor results in more-potent suppression of HCV replication than either drug alone, and could increase the barrier against the development of resistance. For example, Standring et al. found that the combination of the protease inhibitor boceprevir and the nucleoside analog valopicitabine suppressed the emergence of resistance to either drug[69]. A variety of different three-drug combinations have also been shown to have additive or synergistic effects on HCV activity in vitro[70]. Such combination therapy is still in the very early stages of development, and it will be several years before these in vitro results can be tested in large-scale clinical trials.

Novel anti-HCV agents belonging to all the new classes are being tested in combination with peginterferon α, with or without RBV. Viral suppression with such combination therapy has been superior to that with monotherapy in all cases. The combination of an antiviral agent with peginterferon α plus RBV seems to reduce the rapid selection of drug-resistant HCV strains— as reported in a study of telaprevir[71]. Despite the tremendous potential of the new antiviral agents, many questions remain to be answered regarding their use, especially within the context of the current standard of care. Careful research is required to balance the unmet need of patients on the one hand and the requirements of comprehensive clinical development programs on the other.

Conclusion

Peginterferon α plus RBV is the current standard of care for patients with chronic HCV infection, and is likely to remain the cornerstone of therapy for some considerable time to come. The determination of viral response to therapy is a relatively simple and reliable tool that facilitates the tailoring of treatment to the individual patient. More-sophisticated and more-detailed models of HCV response to therapy continue to be developed; these models offer new insights into the mechanisms of antiviral therapy and provide a means to compare different treatment regimens and responses in different patient populations.

The development of HCV-specific antiviral compounds has the potential to provide new options for the treatment of patients with chronic hepatitis C. The results from early clinical trials imply that a number of these agents are safe, well tolerated, and have potent antiviral activity that results in a rapid decline in HCV RNA levels. At least in the early stages, it is likely that these new agents will be used in combination with the current standard of care. The rapid decline in HCV RNA levels induced by the new anti-HCV agents in such combination therapy is promising, given that evidence suggests that an RVR to peginterferon α plus RBV is associated with a greater likelihood of achieving SVR and the possibility of shortened treatment duration. Given the risk of treatment resistant mutations developing, future research will focus on the development not only of new compounds but also of optimum drug combinations that aim to avoid selection of resistant strains enhance the effectiveness of treatment, reduce the duration of treatment, and potentially improve tolerability.

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