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Drugs in Development for Hepatitis C

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Abstract

Currently available anti-hepatitis C virus (HCV) therapy is effective in only half of infected patients and is limited by adverse effects that often necessitate discontinuation. Therefore, new treatments are being developed, including optimization of current standard treatment with peginterferon plus ribavirin, specifically targeted antiviral therapy for HCV, novel immunomodulatory agents and treatments aimed at reducing fibrosis. This review focuses on novel anti-HCV drugs that are currently in an advanced stage of clinical development. Albinterferon-α-2b, a fusion molecule of albumin and interferon-α-2b, has a longer half-life than peginterferon, which enables a bi-weekly administration interval. Preliminary data indicate similar response rates for albinterferon-α-2b plus ribavirin compared with peginterferon-α-2b plus ribavirin, but possible benefits with respect to quality of life. Telaprevir, a NS3/4 protease inhibitor, demonstrated a rapid and profound antiviral effect in phase I trials that was synergistic with that of peginterferon-α-2a. Recently completed phase II trials on triple combination treatment with telaprevir, peginterferon-α-2a and ribavirin given for 12–24 weeks reported sustained virological response in up to 68% of patients with treatment-naive HCV genotype 1 infection.

It is estimated that approximately 3% of the world's population is infected with hepatitis C virus (HCV). In developed countries, chronic hepatitis C is the leading cause for cirrhosis, hepatocellular carcinoma and liver transplantation. Antiviral treatment of chronic HCV infection has greatly improved since the introduction of interferon-α treatment of chronic non-A-non-B hepatitis in 1986.[1] Current pegylated interferon (peginterferon) plus ribavirin treatment provides a cure rate of 40–90%, depending on HCV genotype. Besides limited efficacy, this treatment is associated with significant adverse effects that frequently necessitate its discontinuation. Therefore, treatments with higher efficacy and/or better tolerability are needed.

Elucidation of the HCV genome has enabled the identification of new targets and approaches for anti-HCV drugs. The availability of a sub-genomic replicon system and, more recently, of a full-length HCV genome that replicates and produces infectious viral particles now facilitates screening of candidate drugs.[2-4] Consequently, many new antiviral compounds have been synthesized, but few have entered clinical trials. Some drugs with promising antiviral effects in early clinical studies have subsequently shown problems of toxicity and their further development has been halted. This review, rather than providing a complete list of investigational substances in the HCV pipeline, gives an overview on novel antiviral strategies against HCV, focusing

on drugs that have already entered an advanced stage of clinical development.

1. Specifically Targeted Antiviral Therapy for Hepatitis C Virus (HCV)

The HCV genome consists of a single open reading frame of approximately 9.6 kilobases. The 5′ untranslated region (UTR) contains an internal ribosome entry site (IRES) that initiates translation of a 3000 amino acid polyprotein, which is subsequently processed by viral and host proteases into various structural and nonstructural proteins (figure 1). Several potential targets have been identified for HCV-specific antiviral drugs, including IRES, E1/E2, p7, NS2, NS3, NS5A and NS5B,[5,6] and many orally administered small-molecule inhibitors of these targets are being developed (table I).[7-10]

1.1 Nucleic-Acid-Based Antiviral Agents

Various synthetic nucleic acids that target parts of the HCV genome have been designed as antiviral agents. They have to be administered parenterally and include ribozymes, antisense oligonucleotides and short interfering RNA (siRNA). The HCV IRES has been considered the most attractive target for these approaches as it is highly conserved among HCV genotypes.

1.1.1 Ribozymes

Ribozymes are small RNA molecules that can specifically bind to complimentary RNA sequences and catalyse the cleavage of the target RNA. The ribozyme RPI.13919, designed to cleave the HCV IRES from the 5′-UTR region of the HCV genome, showed moderate antiviral efficacy in a phase II trial, but further development was stopped because of severe toxicity in primates.[11]

1.1.2 Antisense Oligonucleotides

Antisense oligonucleotides are synthetic stabilized DNA nucleic acid sequences that specifically bind to complimentary RNA, resulting in inhibition of RNA translation and protein expression. One compound, ISIS 14803, is a 20-base antisense oligonucleotide complementary to the IRES, which is important for translation initiation. In a phase I trial, a 4-week treatment with escalating doses of ISIS 14803 produced modest antiviral effects (transient HCV RNA reductions of 1.2–1.7 log in 3 of 28 patients), but ALT flares in a larger proportion of patients (ALT >10 times the upper limit of normal in 5 of 28 patients) raised important safety concerns.[12]

1.1.3 RNA Interference

RNA interference by siRNA is a natural process used by eukaryotic cells to recognize and destroy abnormal or exogenous RNA. Chemically modified siRNA may be used therapeutically to silence specific gene expression. Efficient suppression of HCV replicon RNA has been demonstrated with various siRNAs, but problems of delivery and resistance currently limit their use in clinical trials.[13]

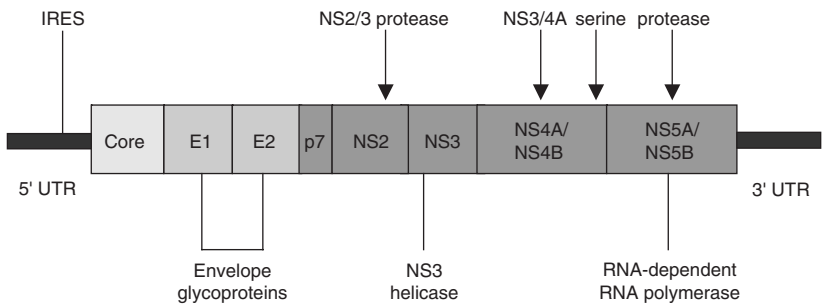

Fig. 1. Schematic representation of the hepatitis C virus genome and targets for current drug development. **IRES** = internal ribosome entry site; **UTR** = untranslated region.

Table I. Targeted anti-hepatitis C virus drugs under clinical development

Drug	Manufacturer	Stage of development
Nucleic-acid-based antiviral agents		
RPI.13919	Ribozyme Pharmaceuticals	Halted
ISIS 14803	ISIS Pharmaceuticals	Halted
NS3/4A serine protease inhibitors		
Ciluprevir (BILN 2061)	Boehringer Ingelheim	Halted
Telaprevir (VX-950)	Vertex	Phase II
Boceprevir (SCH 503034)	Schering-Plough	Phase II
GS-9132 (ACH-806)	Achillion/Gilead	Halted
TMC 435350	Tibotec	Phase I
ITMN-191 (R7227)	InterMune/Roche	Phase I
MK-7009	Merck Sharpe & Dohme	Phase I
NS5A inhibitors		
A-831	Arrow Therapeutics/AstraZeneca	Phase I
NS5B RNA-dependent RNA-polymerase inhibitors		
nucleoside analogues		
Valopicitabine (NM283)	Idenix/Novartis	Halted
R1626 (prodrug of R1479)	Roche	Phase II
R7128 (PSI-7081)	Pharmasset/Roche	Phase I
non-nucleoside analogues		
JTK-003	Japan Tobacco	Halted
R803	Rigel	Halted
Nesbuvir (HCV-796)	ViroPharma/Wyeth	Halted
BILB1941	Boehringer Ingelheim	Phase I
GS-9190	Gilead	Phase I
Cyclophilin inhibitors		
DEBIO-25	Debiopharm	Phase I

1.2 NS3/4A Protease Inhibitors

The HCV polyprotein is post-translationally processed by proteases into structural and nonstructural proteins. The NS3/4A protease, a member of the chymotrypsin serine protease family, which cleaves the viral polyprotein at four junctions with a temporal sequence that is crucial for HCV replication, is the target of many novel small-molecule inhibitors.[14,15]

1.2.1 Ciluprevir

Ciluprevir (BILN 2061) was the first specific NS3/4A serine protease inhibitor evaluated in clinical trials in patients with chronic hepatitis C. Oral short-term administration for 2 days was well tolerated and produced 2–3 log decrease in viraemia in treatment-naive patients with HCV genotype 1,[16,17] but a less pronounced and more variable response in genotype 2/3 patients.[18] These studies provided proof-of-concept that protease inhibitors are effective in patients with chronic hepatitis C and demonstrated that response depends on HCV genotype. However, further development of ciluprevir has been stopped because of cardiac toxicity observed in animals.[19]

1.2.2 Telaprevir

Telaprevir (VX-950) is a peptidomimetic inhibitor of NS3/4A protease that includes an α-ketoamide moiety anchoring at the active site. In a phase Ib trial in 34 patients with chronic genotype 1 HCV infection (mostly nonresponders to previous antiviral treatment), telaprevir monotherapy reduced HCV RNA by 3.5–4.8 log in a dose-dependent fashion. In this trial, patients were treated for

14 days with placebo or telaprevir at three different doses (450 mg every 8 hours, 750 mg every 8 hours or 1250 mg every 12 hours). At the 750 mg dose (the dose with the highest trough plasma drug concentrations), HCV RNA dropped markedly by 4.4 log after 14 days. Mild gastrointestinal symptoms were noted as adverse events.[20] However, early virological breakthrough (starting between days 3 and 7 of administration) was observed in some patients that was related to the emergence of resistant variants.[21] In previously untreated patients with chronic genotype 1 HCV infection, combination treatment with telaprevir (750 mg every 8 hours) plus peginterferon-α-2a yielded a median 5.5 log reduction in HCV RNA after 14 days,[22,23] indicating additive effects of telaprevir and peginterferon-α-2a (figure 2). Importantly, HCV mutants resistant to telaprevir remained sensitive to peginterferon-α-2a.[22]

Recently completed phase II trials yielded very encouraging results for triple combination treatment with telaprevir, peginterferon-α-2a and ribavirin. In the PROVE-1 trial, 250 treatment-naive HCV genotype 1 patients, enrolled in 37 US centres, were randomized into four groups: three groups treated with telaprevir 750 mg every 8 hours plus peginterferon-α-2a 180 μg/week plus ribavirin 1000–1200 mg/day for 12 weeks followed by 0, 12 or 36 weeks of peginterferon-α-2a plus ribavirin, and a control group treated with peginterferon-α-2a plus ribavirin for 48 weeks. A planned interim analysis was performed when the first 80 enrolled subjects had completed 12 weeks of treatment. At week 12, HCV RNA was undetectable in 88% of patients in the pooled telaprevir groups versus 52% in the control group. Adverse events associated with telaprevir included gastrointestinal events, allergic skin reactions (in several cases severe) and anaemia. Discontinuation because of adverse events was more common in the telaprevir groups (9% vs 3% in the placebo group).[24] The PROVE-2 trial in 323 treatment-naive HCV genotype 1 patients has a similar design except for inclusion of a telaprevir plus peginterferon-α-2a 12-week dual combination group. At week 12, undetectable HCV RNA was observed in 79% with telaprevir plus peginterferon-α-2a plus ribavirin, in 63% with peginterferon-α-2a plus telaprevir, and in 43% with peginterferon-α-2a plus ribavirin.[25]

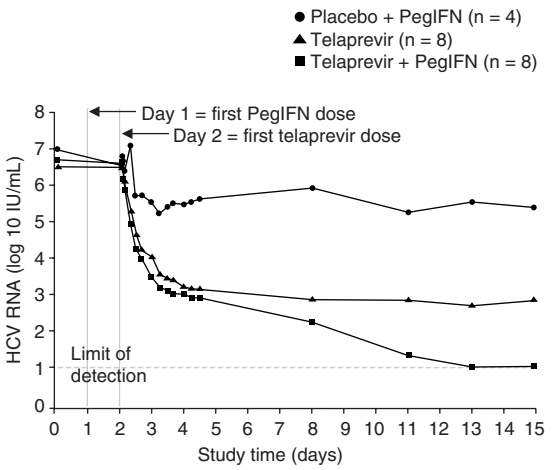

Fig. 2. Antiviral effect of 14-day combination treatment with telaprevir (VX-950) plus peginterferon-α-2a (PegIFN) in treatment-naive hepatitis C virus (HCV) genotype 1 patients. Telaprevir was administered at 750 mg every 8 hours from day 2 to day 15, and PegIFN 180 μg was injected subcutaneously on day 1 and day 8. Teleprevir plus PegIFN led to a median 5.5 log decline of HCV RNA at day 15 and no viral breakthrough occurred in this group (reprinted from Forestier et al.,[23] © 2007, with permissions of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

Final results of the PROVE trials recently became available at the European Association for the Study of the Liver (EASL) 2008 meeting in Milan, Italy. For PROVE-1, sustained virological response (SVR) was 35% in the 12-week treatment arm, 61% in the 24-week treatment arm, 67% in the 48-week treatment arm and 41% in the control arm.[26] For PROVE-2, SVR was 36% in the 12-week (no ribavirin) arm, 62% in the 12-week (triple) arm, 68% in the 24-week treatment arm and 48% in the control arm.[27] Thus, in HCV genotype 1 patients, 24-week telaprevir-based regimens resulted in a 20% higher SVR than previously achieved with 48-week standard treatment with peginterferon plus ribavirin. Maculopapular rash (mostly occurring between day 60 and day 90 of treatment) and anaemia were the most important adverse effects of telaprevir.

1.2.3 Boceprevir

Boceprevir (SCH 503034) is another peptidomimetic NS3/4 protease inhibitor with high

antiviral activity *in vitro* in the replicon system. In a phase Ib study in HCV genotype 1 nonresponders to previous peginterferon-α-2b plus ribavirin therapy, boceprevir 400 mg every 8 hours plus weekly peginterferon-α-2b 1.5 μg/kg given for 2 weeks produced a 2.9 log decline in HCV RNA compared with a 1.6 log decline with boceprevir alone and a 1.3 log decline with peginterferon alone.[28] In this study, detailed virological testing revealed an additive effect of boceprevir over peginterferon-α-2b.

Interim results of the SPRINT-1 study, an ongoing phase II trial with boceprevir in 595 treatment-naive HCV genotype 1 patients, were recently presented as a late-breaking abstract at the EASL 2008 meeting.[29] Triple combination treatment with boceprevir 800 mg every 8 hours, peginterferon-α-2b 1.5 μg/kg and ribavirin 800–1400 mg/day for 24 weeks resulted in an early virologic response (week 12) of 78% versus 34% in patients receiving dual therapy with peginterferon plus ribavirin. SVR12 (i.e. 12 weeks after cessation of treatment) was 57% in the 24-week triple arm. Gastrointestinal events, anaemia and dysgeusia were the most common adverse events.

1.2.4 Other Protease Inhibitors

The development of GS-9132 (ACH-806), which inhibits HCV replication via binding to NS4A, has been stopped because of nephrotoxicity in a clinical trial.[30] Administration of TMC 435350 (200 mg once daily for 5 days) to six HCV genotype 1 nonresponders was well tolerated and showed a promising median 3.9 log decline in HCV RNA.[31] ITMN-191 (R7227) and MK7009 are currently being studied in phase I trials.

1.3 NS5A Inhibitors

NS5A inhibitors target NS5A, a HCV nonstructural protein that seems to be essential for viral RNA production and is well conserved across HCV genotypes. A-831 is an inhibitor of the NS5A protein with potent antiviral activity in the replicon system and is currently being investigated in a phase I trial.[32]

1.4 Nucleoside Analogue NS5B Polymerase Inhibitors

Nucleoside analogue polymerase inhibitors target the catalytic site of the HCV RNA-dependent RNA polymerase and are incorporated into the elongating RNA strand as chain terminators.[7]

1.4.1 Valopicitabine

Valopicitabine (NM283) is an orally bioavailable prodrug of 2′-C-methylcytidine, a specific nucleoside analogue inhibitor of HCV polymerase.[33] This drug is the first polymerase inhibitor to show antiviral activity in humans as a reduction in viraemia by 0.7–1.0 log after a 2-week course demonstrated in a phase I trial. A subsequent phase IIb trial enrolled 178 patients with chronic HCV (genotype 1, nonresponders to peginterferon-α plus ribavirin) who received various doses of valopicitabine up to 800 mg/day along with peginterferon-α-2a or peginterferon plus ribavirin (control group) for 48 weeks. At week 24, HCV RNA decreased by 3.3 log versus 2.3 log with peginterferon-α plus ribavirin treatment.[34] In 173 treatment-naive HCV genotype 1 patients, combination treatment with peginterferon-α-2a and valopicitabine led to a 3.7–4.4 log reduction in HCV RNA after 36 weeks.[35] Unfortunately, valopicitabine was associated with significant gastrointestinal toxicity, including severe diarrhoea with dehydration that required hospitalization in some individuals, at the highest dose of 800 mg/day. Furthermore, *in vitro* studies suggest that antiviral efficacy of valopicitabine is inhibited by ribavirin.[36] Therefore, further clinical development of this drug has been suspended.

1.4.2 R1626

R1626 is a prodrug of the nucleoside analogue R1479 (4′-azidocytidine), a potent inhibitor of HCV replication *in vitro*. A dose ascending study was performed in treatment-naive chronic HCV genotype 1 patients and the highest dose (4500 mg every 12 hours) led to a mean 3.7 log decrease in HCV RNA levels after 14 days of treatment, which represents the greatest viral load reduction so far reported among this class of antiviral agents.[37] However,

dose-dependent haematological adverse effects were observed. A phase IIa study in 104 treatment-naive HCV genotype 1 patients demonstrated a mean 5.2 log decline of HCV RNA after 4 weeks of triple combination treatment with R1626 (1500 mg twice daily) plus peginterferon-α-2a plus ribavirin versus a mean 2.4 log decline only with standard peginterferon-α-2a plus ribavirin treatment, indicating a robust synergistic antiviral effect.[38] In a further interim analysis of this trial, an encouraging end-of-treatment response rate of 84% with continued peginterferon plus ribavirin treatment until week 48 was reported, indicating that the antiviral effect of the initial 4-week triple combination with R1626 was sustained.[39]

1.4.3 R7128

R7128 (PSI-7081) is a prodrug of PSI-6130, an oral nucleoside analogue polymerase inhibitor. In a phase I trial in 40 nonresponders to interferon-based treatment, monotherapy with R7128 1500 mg twice daily resulted in a mean 2.7 log decline of HCV RNA after 14 days. Treatment was well tolerated, with headache as the most common adverse event.[40] Preliminary data on triple combination treatment with R7128 (500 mg twice daily) plus peginterferon-α-2a plus ribavirin for 28 days showed a mean 5.1 log HCV RNA decline in 20 treatment-naive HCV genotype 1 patients.[41]

1.5 Non-Nucleoside NS5B Polymerase Inhibitors

The non-nucleoside polymerase inhibitors bind allosterically at different sites on the surface of the HCV RNA-dependent RNA polymerase and alter its structure and function by freezing the enzyme in the 'open', inactive configuration.[7]

1.5.1 Nesbuvir

Monotherapy with nesbuvir (HCV-796) has demonstrated clinical antiviral activity across multiple HCV genotypes. Combination treatment with nesbuvir (100–1000 mg every 12 hours) plus peginterferon-α-2b (1.5 μg/kg) in treatment-naive HCV patients produced a mean 3.3–3.5 log reduction of viral load versus 1.6 log with peginterferon-α-2b monotherapy at day 14. No dose-limiting toxicity of nesbuvir was observed.[42] However, an ongoing phase II trial with peginterferon-α-2b plus ribavirin plus nesbuvir triple combination treatment was stopped in August 2007 because of possible hepatic toxicity.[43]

1.5.2 Other Non-Nucleoside NS5B Polymerase Inhibitors

JTK-003 and R803 were highly potent *in vitro* but failed to show antiviral activity when administered to patients. BILB1941 tested in 96 HCV genotype 1 patients at doses ranging from 10 mg every 8 hours to 450 mg every 8 hours over 5 days showed antiviral activity, but gastrointestinal adverse effects precluded testing of higher doses.[44] GS-9190 was administered to 31 treatment-naive HCV genotype 1 patients at single ascending doses (40–480 mg), which were well tolerated and produced median 0.5–1.5 log declines of HCV RNA after 24 hours.[45]

1.6 Cyclophilin Inhibitors

Cyclophilins are ubiquitous intracellular proteins that are involved in protein folding. Cyclophilin B has been shown to serve as a cellular cofactor of the NS5B RNA-dependent RNA polymerase and, thus, is important for HCV replication.[46] The cyclophilin inhibitor SDZ811 (NIM811) is a ciclosporin analogue that binds to cyclophilins but not to calcineurin and has been found to exert a strong antiviral activity *in vitro*.[47]

1.6.1 DEBIO-025

The cyclophilin inhibitor DEBIO-025 exhibits dual antiviral activity against HIV-1 and HCV. In a phase I trial in HCV/HIV co-infected patients, DEBIO-025 administered at 1200 mg every 12 hours for 14 days produced a 1.0 log decline for HIV-1 viral load and a 3.6 log decline for HCV RNA.[48] Transient hyperbilirubinaemia and thrombocytopenia were the most striking adverse effects.

1.7 Resistance Mutations

A limiting factor for the efficacy of anti-HCV therapies targeted against the viral protease or the viral polymerase is the emergence of resistance.

Table II. Mutations against protease and polymerase inhibitors identified through *in vitro* investigations and those confirmed or additionally found through *in vivo* studies[21,28,50-61]

Drug	*In vitro* mutations	*In vivo* mutations
Protease inhibitors		
Telaprevir	A156S/T/V	V36A/M, T54A, R155K/T, A156S/T/V
Boceprevir	T54A, A156S/T, V170A	T54A
ITMN-191	V23A, Q41R, F43S, S138T, A156S/V, D168A/V/E, S489L	NA
SCH6	R109K, A156V/T	NA
Ciluprevir	R155Q, A156V/T, D168V/A	NA
Polymerase inhibitors		
Nesbuvir (HCV-796)	C316F/Y, S365T/A	C316Y
R1479 (prodrug = R1626)	S96T, S96T/N142T	NA
MK-0608	S282T	NA
A-782759	H95Q, N411S, M414L/T, Y448H	NA
JTK-109	P495L/A	NA
Valopicitabine	S282T	NA

NA = no data available.

Because of the high replication rate of HCV and the lack of proof reading by its RNA-dependent RNA polymerase, mutations accumulate throughout the viral genome generating remarkable sequence variation in the HCV population. From these viral quasispecies, drug-resistant virus may be selected in patients with specifically targeted antiviral therapies. When viral suppression is incomplete, a rapid selection of drug-resistant HCV variants is to be expected, with variants with higher replication capacity having a higher probability of selection.[49]

It is generally accepted that the risk of resistance is inevitable with the emergence of therapies that directly target the HCV replication cycle. Resistance mutations have been shown to develop *in vitro* in the presence of specifically targeted antiviral therapies for HCV, and the development of several resistance mutations has been confirmed and additional mutations have been found through *in vivo* studies recently (table II). Development of resistance with viral breakthrough after initial viral suppression has been recently reported during 14 days of treatment with telaprevir, and a correlation between the trough plasma drug concentration and both the degree of viral suppression and the therapeutic outcome was observed.[50]

The replicative fitness of resistant variants seems to be diminished.[22,50] However, minor populations of pre-existing, resistant variants may have a fitness advantage over the wild type virus in the presence of a drug and become the dominant viral species.[21,51,52,62] After withdrawal of the drug, reversion to the wild type has been observed.[20] Moreover, cross resistance between drugs acting on similar targets has been reported.[21] This may be overcome by the addition of inhibitors against a different HCV protein or nucleic acid target, and the inclusion of an immune-based therapy. Finally, adherence to therapy is a major issue to prevent emergence of resistance. Similar to anti-HIV therapy, the maintenance of the trough concentration of a specific drug through timely administration is essential.

2. Novel Immunomodulatory Agents

While vigorous and multispecific CD4+ and CD8+ T-cell responses are usually present during acute hepatitis C and are associated with viral clearance, T-cell effector function appears to be impaired in chronic hepatitis C.[63-65] Restoration of (innate and adaptive) immune response currently represents the mainstay and will remain an important component of anti-HCV treatment.

2.1 New Interferons

2.1.1 Albinterferon-α-2b

Albinterferon-α-2b (albumin-interferon-α-2b) is an 86 kDa fusion molecule of interferon-α-2b and human serum albumin with an extended half-life of approximately 150 hours that supports administration every 2–4 weeks.[66] Albinterferon-α-2b may offer the benefits of less frequent administration and a possibly improved safety profile.[67] Dose-dependent antiviral activity and good tolerability were observed in both nonresponders to previous interferon-based treatment and treatment-naive HCV genotype 1 patients.[68,69] Preliminary results of a phase II trial in 115 nonresponders to previous interferon-α-based treatment indicate a substantial virological response to albinterferon-α-2b (900–1800 μg every 2 weeks) plus ribavirin 1000–1200 mg/day (end-of-treatment response 25–43%; SVR 9–30%).[70] In a phase IIb trial in 458 treatment-naive HCV genotype 1 patients, albinterferon-α-2b 900 μg every 2 weeks, 1200 μg every 2 weeks, 1200 every 4 weeks and peginterferon-α-2a 180 μg once a week, each with ribavirin 1000–1200 mg/day, achieved similar antiviral efficacy (SVR 59%, 56%, 51% and 58%, respectively) but quality of life as estimated by the Short Form-36 Health Survey was significantly more favourable in the albinterferon-α-2b 900 μg every 2 weeks arm.[71]

2.1.2 Omega Interferon

Omega interferon is a new type-1 interferon that has been designed for continuous delivery by an implantable device. Preliminary data of a phase II trial in interferon-naive patients with chronic HCV genotype 1 infection indicate an EVR of 60% versus 84% and a SVR12 of 6% versus 36% in patients receiving subcutaneous omega interferon 25 μg daily with or without ribavirin (1000–1200 mg/day), respectively.[72]

2.1.3 Controlled-Release Recombinant Interferon-α-2b

A controlled-release recombinant interferon-α-2b (Locteron™)[1] has been developed that contains interferon-α-2b (BLX-883) attached to biodegradable microspheres providing slow release of interferon-α-2b without an initial burst and thus allowing a 2-week administration interval.[73] In a phase IIa trial in 32 treatment-naive HCV genotype 1 patients, controlled-release recombinant interferon-α-2b 640 μg every 2 weeks plus weight-based ribavirin led to a mean 4.7 log HCV RNA decline after 12 weeks with a favourable safety and tolerability profile.[74]

2.2 Ribavirin Analogues

As tolerability of ribavirin is frequently limited by marked haemolytic anaemia, analogues lacking this adverse effect are being sought.[75]

2.2.1 Taribavirin

Taribavirin (viramidine) is a liver targeted prodrug of ribavirin that is converted to ribavirin in the liver and does not significantly accumulate in erythrocytes. In a phase II trial, taribavirin (400–800 mg twice daily) combined with peginterferon-α-2a showed a similar antiviral effect at week 24 but significantly less haemolytic anaemia than ribavirin.[75,76] The highest SVR was observed with a dose of 600 mg twice daily (SVR 37% vs 44% with ribavirin [1000–1200 mg/day]). The fixed taribavirin dose of 600 mg twice daily was therefore chosen for phase III studies.

The results of two large phase III studies in treatment-naive HCV patients (VISER-1 and VISER-2) were recently reported in abstract form. VISER-1 included 970 patients randomized to taribavirin 600 mg twice daily or ribavirin 1000–1200 mg/day in combination with peginterferon-α-2b. In the taribavirin group, the rate of anaemia (5% vs 24%) but, unfortunately, also SVR (38% vs 52%) were significantly lower than in the ribavirin group.[77] VISER-2 was a study with similar design using peginterferon-α-2a instead of peginterferon-α-2b and yielded comparable results (anaemia rate 6% vs 22%; SVR 40% vs 55%). From these studies, it was concluded that weight-based administration of taribavirin should be employed

1 The use of trade names is for product identification purposes only and does not imply endorsement.

and a new phase IIb trial was designed using taribavirin 20 vs 25 vs 30 mg/kg per day.[78]

2.3 Inosine 5′-Monophosphate Dehydrogenase Inhibitors

Inhibitors of inosine 5′-monophosphate dehydrogenase (IMPDH) are being evaluated as antiviral drugs because this enzyme catalyses an essential step in the biosynthesis of guanine nucleotides.[79]

2.3.1 Merimepodib

Merimepodib (VX-497) is a noncompetitive inhibitor of IMPDH. In treatment-naive chronic hepatitis C patients, a 4-week course of interferon-α plus merimepodib combination treatment did not significantly affect viraemia compared with interferon-α alone.[80] In contrast, in nonresponders to interferon-α plus ribavirin, the addition of merimepodib to peginterferon-α-2b plus ribavirin significantly improved on-treatment response at week 24.[79]

2.4 Toll-Like Receptor Agonists

Toll-like receptors (TLRs) sense the presence of invading micro-organisms through the recognition of characteristic molecular patterns. Signalling by stimulated TLRs initiates production of pro-inflammatory cytokines and chemokines. TLR3, 7, 8 and 9 seem to be responsible for the detection of viral molecules. Stimulation of the appropriate TLR may restore the innate and adaptive immune response, which is usually dysfunctional in HCV-infected hosts.[81]

2.4.1 Resiquimod

Resiquimod is a small molecule that signals through TLR7 causing induction of cytokines including interferon-α, interleukin (IL)-12 and tumour necrosis factor (TNF)-α. Pilot studies showed a modest transient reduction in HCV RNA levels.[82]

2.4.2 Isatoribine (ANA245)

Isatoribine (ANA245) is a guanosine analogue TLR7 agonist. In a proof-of-concept study in 12 chronic hepatitis C patients, subcutaneous administration of isatoribine for 7 days caused a 0.8 log decrease of HCV RNA.[83] However, studies with isatoribine and its oral prodrug, ANA975, were suspended for safety reasons (intense immune stimulation in animals).

2.4.3 CPG 10101

CPG 10101, a synthetic oligodeoxynucleotide, is a TLR9 agonist stimulating antiviral cytokine production by B cells and plasmacytoid dendritic cells. In a phase Ib trial, CPG 10101 administered subcutaneously once or twice a week for 4 weeks resulted in a dose-dependent cytokine induction paralleled by a decrease in HCV RNA (average 1.7 log reduction at the highest dose),[84] which was similar to that previously observed with peginterferon-α monotherapy. However, despite these encouraging results, further clinical development of CPG 10101 was suspended because of economic considerations.[81]

2.5 Other Immunomodulators

2.5.1 Interleukin-12

IL-12 is an immunomodulatory cytokine that stimulates proliferation of activated cytotoxic T lymphocytes and natural killer cells as well as interferon-α production. Recombinant IL-12 was studied in a placebo-controlled study in 225 nonresponding chronic hepatitis C patients and resulted in SVR in only 1% of the patients; in contrast, 3% developed severe adverse events including chills, fever, fatigue, headache and arthralgia, resulting in early termination of the trial.[85] Thus, because of its poor efficacy and substantial toxicity, IL-12 is unlikely to provide an alternative to conventional interferon-based therapy.

2.5.2 Tumour Necrosis Factor Antagonists

TNF antagonists may modulate inflammation in chronic hepatitis C. In 50 patients with chronic hepatitis C, etanercept given as an adjuvant to interferon-α plus ribavirin resulted in an increased on-treatment virological response at week 24 (etanercept 63% vs placebo 32%) as well as an attenuation of adverse effects.[86]

3. Treatments Aimed at Reducing Fibrosis

Where eradication of HCV is not possible, prevention of fibrosis progression remains another important endpoint of therapy. To this end, studies with long-term peginterferon monotherapy are currently ongoing. Unfortunately, preliminary data of low-dose peginterferon-α-2a (90 μg/week) over 3.5 years within the HALT-C (hepatitis C antiviral long-term treatment against cirrhosis) trial failed to show a beneficial effect on fibrosis progression when compared with placebo.[87]

3.1 Interferon-γ

Experimental studies suggest that interferon-γ can inhibit the proliferation of hepatic stellate cells and reduce collagen synthesis. However, in a randomized controlled trial in 502 chronic hepatitis C patients with advanced fibrosis, subcutaneous interferon-γ-1b (100–200 μg three times a week) for 48 weeks showed no benefit over placebo.[88]

3.2 Caspase Inhibitors

Caspases are proteases that mediate apoptosis. Therefore, caspase inhibitors could improve hepatic fibrosis via inhibition of apoptosis. The pancaspase inhibitor emricasan (IDN-6556; PF-03491390) was recently shown to reduce ALT levels but had no effect on HCV RNA.[89] Whether this approach is effective in reducing hepatic fibrosis, remains to be determined.

4. Conclusion

Whereas past research has focused on the optimization of interferon-α plus ribavirin-based antiviral treatment, many new specific anti-HCV drugs have been designed and several of those have reached the stage of clinical development. However, the development of many new anti-HCV drugs that showed high initial efficacy in phase I trials has meanwhile been halted because of safety issues or for economic considerations. At present, adding a new specifically targeted antiviral therapy for HCV (STAT-C) drug on to peginterferon-α plus ribavirin standard treatment seems to be the most promising strategy.

Given the high error rate of HCV polymerase, resistance mutations may develop very early and frequently, and even though viral fitness is limited in these variants, this will severely limit the efficacy of HCV-specific antiviral compounds. Therefore, testing HCV for drug resistance will become a necessity in the future and therapies will be individualized on the basis of the resistance report generated. Combination of different (not cross-resistant) antiviral compounds might allow resistance to be overcome, as is the case in HIV infection. Apart from STAT-C, stimulation of the innate and adaptive immune response will remain an important component of antiviral treatment. Besides development of new drugs, future research will focus on establishing the optimal combination of drugs (STAT-C drugs plus immunomodulators) that would allow shorter, while more effective, treatment.

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