New Hepatitis C Therapies in Clinical Development

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Abstract
With the current standard of care for the treatment of chronic hepatitis C, a combination of pegylated interferon alfa and ribavirin, sustained virologic response rates can be achieved in approximately 50% of patients only.

Improved understanding of the viral life cycle has led to the identification of numerous potential targets for novel, direct-acting antiviral compounds. Inhibitors of the NS3/4A protease are currently the most advanced in clinical development. Recently completed phase 3 studies of the two protease inhibitors telaprevir and boceprevir, each given in combination with standard of care, yielded sustained virologic response rates in the range of 66-75% in treatment-naive patients and 59-66% in treatment-experienced patients with HCV genotype 1 infection. Studies of second-generation protease inhibitors, with the potential advantage of improved potency, drug metabolism and pharmacokinetics profile, are already underway.

Inhibitors of the HCV NS5A protein and NS5B polymerase are potentially active across different HCV genotypes and have shown promising antiviral efficacy in early clinical studies. Other emerging mechanisms include silymarin components and inhibitors of cell proteins required for HCV replication.

While improved formulations of current HCV therapies are also being developed, future hopes lie on the combination of direct-acting antivirals with the eventual possibility of interferon-free treatment regimens.

Key words: chronic hepatitis C; direct-acting antivirals; protease inhibitor; polymerase inhibitor; NS5A inhibitor; cyclophilin inhibitor.

INTRODUCTION
Chronic infection with the hepatitis C virus (HCV) affects more than 3% of the world’s population [1]. There are about 4 million carriers in Europe alone who are at risk of developing advanced liver fibrosis, cirrhosis and hepatocellular carcinoma.

With the current standard of care (SOC; pegylated interferon [PEG-IFN] alfa and ribavirin [RBV]), only 40-50% of patients with HCV genotype 1 infection and about 80% of patients with HCV genotype 2 or 3 infection can be cured [2-5]. In addition, long treatment durations and therapy-associated side effects such as severe cyopenia, flu-like symptoms or depression are associated with treatment discontinuation in a significant number of patients.

Recent advances in the development of HCV cell culture systems and replication assays have improved our understanding of the viral life cycle, thus leading to the identification of numerous potential targets for novel HCV therapies [6-9]. Indeed, every step of the HCV life cycle may be used as a therapeutic target. However, direct-acting antivirals that target post-translational processing of the HCV polyprotein and inhibitors of the HCV replication complex are currently the most advanced in clinical development, with studies ranging from pre-clinical to phase 3. Other promising therapeutic targets include cell proteins that are required for HCV replication such as cyclophilins. Finally, improvements of current therapies, such as new interferon and ribavirin formulations are also in active development.

In this review, we will give an overview of recent advances in HCV drug discoveries with a special emphasis on direct-acting antivirals that have progressed to phase 2-3 clinical development with anticipated higher cure rates and shorter treatment durations compared to standard therapy (Table 1). Approval of the first DAs is expected by mid-2011.

ANTIVIRALS TARGETING HCV POLYPEPTIDE PROCESSING

NS3/4A PROTEASE INHIBITORS
The HCV NS3/4A protease has been recognized as an important target for antiviral therapy due to its key role within the HCV life cycle (e.g. cleavage of the genome-encoded polyprotein and inactivation of cellular proteins required for innate immunity) [6].

Inhibitors of the HCV NS3/4A serine protease are currently the furthest along in development and they have shown strong antiviral efficacy but a low genetic barrier to resistance in early clinical studies. Protease inhibitors can be divided into two chemical classes, macrocyclic inhibitors and linear, tetra-peptide α-ke-toamide derivatives (Table 1).

The clinical proof-of-concept for NS3/4A protease inhibitors was achieved with cipluprevir (BILN 2061), a macrocyclic protease inhibitor that showed substantial antiviral activity in patients with HCV genotype 1 [10]. However, cipluprevir was not further developed due to serious cardiotoxicity observed in a monkey model.
Table 1. New HCV therapies in the pipeline.

| Drug name | Company | Target / Active drug | Study phase |
|-----------|---------|----------------------|-------------|
| **NS3/4A protease inhibitors** | | | |
| Ciluprevir (BILN 2061) | Boehringer Ingelheim | Active site / macrocyclic | Stopped |
| Boceprevir (SCH503034) | Merck | Active site / linear | Phase 3 |
| Telaprevir (VX-950) | Vertex | Active site / linear | Phase 3 |
| Danoprevir (RG7227) | Roche | Active site / macrocyclic | Phase 2 |
| TMC435 | Tibotec / Medivir | Active site / macrocyclic | Phase 2 |
| Vaniprevir (MK-7009) | Merck | Active site / macrocyclic | Phase 2 |
| BI 201335 | Boehringer Ingelheim | Active site / linear | Phase 2 |
| BMS-650032 | Bristol-Myers Squibb | Active site | Phase 2 |
| GS-9256 | Gilead | Active site | Phase 2 |
| ABT-450 | Abbott / Enanta | Active site | Phase 2 |
| Narlaprevir (SCH900518) | Merck | Active site / linear | On hold |
| PHX1766 | Phenomix | Active site | Phase 1 |
| ACH-1625 | Achillion | Active site / linear | Phase 1 |
| IDX320 | Idenix | Active site / macrocyclic | On hold |
| MK-5172 | Merck | Active site / macrocyclic | Phase 1 |
| VX-985 | Vertex | Active site | Phase 1 |
| GS-9451 | Gilead | Active site | Phase 1 |
| **Nucleos(t)ide NS5B polymerase inhibitors** | | | |
| Valopicitabine (NM-283) | Idenix / Novartis | Active site / NM-107 | Stopped |
| RG7128 | Roche / Pharmasset | Active site / PSI-6130 | Phase 2 |
| IDX184 | Idenix | Active site | Phase 2 |
| R1626 | Roche | Active site / R1479 | Stopped |
| PSI-7977 | Pharmasset | Active site | Phase 2 |
| PSI-938 | Pharmasset | Active site | Phase 1 |
| INX-189 | Inhibitex | Active site | Phase 1 |
| **Non-nucleoside NS5B polymerase inhibitors** | | | |
| BILB 1941 | Boehringer Ingelheim | NNI site 1 / thumb 1 | Stopped |
| BI 207127 | Boehringer Ingelheim | NNI site 1 / thumb 1 | Phase 2 |
| MK-3281 | Merck | NNI site 1 / thumb 1 | Stopped |
| Filibuvir (PF-00868554) | Pfizer | NNI site 2 / thumb 2 | Phase 2 |
| VX-916 | Vertex | NNI site 2 / thumb 2 | On hold |
| VX-222 | Vertex | NNI site 2 / thumb 2 | Phase 2 |
| VX-759 | Vertex | NNI site 2 / thumb 2 | Phase 1 |
| ANAS98 | Anadyx | NNI site 3 / palm 1 | Phase 2 |
| ABT-333 | Abbott | NNI site 3 / palm 1 | Phase 2 |
| ABT-072 | Abbott | NNI site 3 / palm 1 | Phase 2 |
| Nesbuvir (HCV-796) | ViroPharma / Wyeth | NNI site 4 / palm 2 | Stopped |
| Tegobuvir (GS-9190) | Gilead | NNI site 4 / palm 2 | Phase 2 |
| IDX375 | Idenix | NNI site 4 / palm 2 | Phase 1 |
| **NS5A inhibitors** | | | |
| BMS-790052 | Bristol-Myers Squibb | NS5A domain 1 inhibitor | Phase 2 |
| BMS-824393 | Bristol-Myers Squibb | NS5A inhibitor | Phase 1 |
| AZD7295 | AstraZeneca | NS5A inhibitor | Phase 1 |
| PPI-461 | Presidio | NS5A inhibitor | Phase 1 |
| **Indirect inhibitors / unknown mechanism of action** | | | |
| NIM811 | Novartis | Cyclophilin inhibitor | Stopped |
| SCY-635 | Scynexis | Cyclophilin inhibitor | Phase 1 |
| Alisporivir (Debio-025) | Debiopharm / Novartis | Cyclophilin inhibitor | Phase 2 |
| Alinia (nitazoxanide) | Romark | PKR induction ? | Phase 2 |
| Celgosivir | BioWest | Alpha-glucosidase inhibitor | Stopped |
| **New formulations of current therapies** | | | |
| Taribavirin | Valeant | / ribavirin | Phase 2 |
| Locteron (BLX-883) | Biolex | Interferon receptor type 1 | Phase 2 |
| PEG-rIL-29 (peginterferon lambda) | ZymoGenetics / BMS | Interferon receptor type 3 | Phase 2 |
| Joulferon (albinterferon alfa-2b) | HGS / Novartis | Interferon receptor type 1 | Stopped |
Telaprevir

Telaprevir (VX-950), an orally bioavailable, linear, ketoamide protease inhibitor, was initially investigated given alone or in combination with PEG-IFN alfa-2a ± RBV in patients infected with HCV genotype 1 in a number of short-term studies [11-13]. A median maximum reduction of -5.49 log_{10} IU/ml HCV RNA from baseline was observed in patients treated with telaprevir (750 mg three times daily) plus PEG-IFN alfa for 14 days. Mutations associated with clinical resistance to telaprevir were identified at 4 positions close to the NS3 catalytic domain - V36a/M/l, T34a, R155K/M/S/T, A156S (all three conferring low- to medium-level resistance) and A156T/V (conferring high-level resistance) [14, 15]. Viral rebound due to selected drug-resistant mutants occurred in the majority of patients during monotherapy with telaprevir. However, a reduced frequency of resistant mutations and no viral breakthrough was observed in the combination studies.

Subsequently, the efficacy of telaprevir (750 mg three times daily) in combination with PEG-IFN 2a ± RBV was studied in three large placebo-controlled phase 2b trials in both treatment-naïve (PROVE 1, n = 290; PROVE 2, n = 323) and treatment-experienced patients who had undetectable HCV RNA at week 4 and week 12 of treatment (eRVR, extended rapid virologic response) were eligible to receive 24 total weeks of therapy. Patients who did not meet this criterion but had undetectable HCV RNA at week 24 received 48 total weeks of therapy. The overall SVR rates ranged from 69% in patients who received 8 weeks of telaprevir to 75% in patients who received telaprevir for 12 weeks, compared to 44% in patients who received SOC alone. Nearly 60% (57% and 58%, respectively) of patients in the telaprevir-based study arms were eligible to undergo shortened treatment duration. Relapse rates were 9%, 9% and 28%, respectively. Treatment discontinuation due to drug-related adverse events during the first 12 weeks of overall treatment occurred in 8%, 7% and 4% of patients, respectively.

The ILLUMINATE trial was conducted in treatment-naïve patients to investigate the benefit of longer treatment duration in patients who achieved an eRVR (65%) following 12 weeks of telaprevir-based therapy. In this study, SVR rates were 92% in eRVR patients who received 24 total weeks of therapy compared to 88% in eRVR patients on 48 total weeks of treatment. Taken together, eRVR was identified as a key predictor of SVR and the majority of patients were eligible to undergo shortened treatment duration with equally high SVR rates compared to the standard therapy duration of 48 weeks.

The REALIZE study evaluated the efficacy of a 12-week triple combination treatment regimen followed by 36 weeks SOC or 4-week lead-in with SOC, followed by 12 weeks triple combination therapy, followed by 32 weeks of SOC in treatment-experienced patients with HCV genotype 1 (partial non-responders, ≥2 log_{10} decline in HCV RNA at week 12; null-responders, <2 log_{10} decline in HCV RNA at week 12; and relapers) vs. SOC alone for 48 weeks. SVR rates for the three treatment arms were 64%, 66% and 17%, respectively. Prior relapers achieved SVR rates of 83%-88%, while prior null responders achieved SVR rates in the range of 29%-33%. A response-guided treatment-arm with shortening of treatment duration was not included in this study. Discontinuation due to adverse events occurred in 4% of the combined telaprevir study arms and in 3% of the control group. The relatively low discontinuation rates due to adverse events in all three phase 3 studies may be explained by precise management plans for telaprevir-induced rashes that involved expert dermatologist consultations at each study site.

During triple therapy with telaprevir plus PEG-IFN alfa/RBV, viral breakthrough associated with the selection of resistant variants was observed in 1-5% of treatment-naïve patients and in up to 25% of previous non-responders. Moreover, variants conferring resistance to NS3 protease inhibitors were also detected in patients with viral relapse after the end of treatment. The long-term significance of these resistant variants is unknown but generally a decline in frequency over time has been observed [25]. However, in single patients,
low to medium levels of V36 and A156 variants were observed up to 4 years after telaprevir therapy [26].

**BOCEPREVIR**

In a phase I b study conducted in treatment-experienced patients with HCV genotype 1, administration of boceprevir (200 mg or 400 mg three times daily), a peptidomimetic α-ketoamide HCV protease inhibitor, with or without PEG-IFN alfa-2b resulted in mean maximum reductions of HCV RNA of up to 1.61 log_{10} and 2.88 log_{10} IU/ml, respectively [27]. Subsequently, a number of mutations conferring boceprevir resistance at low to medium levels were discovered in vivo - V36M/A, T54A/S, V55A, R155K/T, A156S, and V170A [28, 29].
As for telaprevir, reduced antiviral activities of boceprevir in HCV genotype 2/3 infected patients were reported.

A higher dose of boceprevir (800 mg three times daily) in combination with PEG-IFN alfa-2b and RBV was subsequently tested in a larger, phase 2 clinical trial (SPRINT-1; n = 595) in treatment-naïve patients with HCV genotype 1 infection [30]. Patients received either all three drugs in combination for 28 or 48 weeks or for 24 or 44 weeks after a previous 4-week lead-in period of PEG-IFN alfa-2b/RBV, or SOC for 48 weeks. SVR rates ranged from 54% for 28 weeks of triple therapy to 75% after a 4-week lead-in period with PEG-IFN alfa-2b/RBV followed by 44 weeks of triple therapy compared to 38% in the control group. Treatment discontinuations due to adverse events (mainly anaemia and gastrointestinal side effects) that occurred throughout the entire study appeared in 9%-19% of patients receiving boceprevir compared to 8% in the control group.

In patients with prior non-response to SOC therapy, the addition of boceprevir to PEG-IFN alfa and RBV showed only slightly increased SVR rates compared to standard therapy in a phase 2b study with suboptimal boceprevir/RBV dosing (14% vs. 2%) [31].

The delayed start of boceprevir by four weeks, during which time patients received four weeks of SOC alone (lead-in), was designed to decrease the probability of resistance development. Among patients with a null-response to the 4-week lead-in treatment period (≤1.0 log_{10} IU/ml HCV RNA reduction), the SVR rate was 25% for patients who continued 24 weeks of triple therapy and 55% for those who received 44 weeks of triple therapy. In contrast, patients who had a >2 log_{10} IU/ml decline in HCV RNA achieved SVR rates of 73%-81%. Thus, virologic response to the lead-in allows for prediction of subsequent treatment success. However, even in lead-in-null-responders a significant improvement in SVR rates following subsequent triple therapy was observed.

In two phase 3 studies, a larger number of treatment-naïve (SPRINT-2; n = 1097) and treatment-experienced (RESPOND-2; n = 403; partial non-responders and relapers only) patients with HCV genotype 1 infection were enrolled to receive a 4-week lead-in period with telaprevir/RBV followed by either 24 or 44 weeks of combination therapy or a response-guided schedule with the possibility of stopping therapy at week 28 or week 36 of overall treatment duration (based on cEVR, defined as HCV RNA negative at week 8 and week 24), respectively [32, 33]. Among treatment-naïve patients, 66% in the 48-week treatment group and 63% in the response-guided therapy group achieved SVR compared to 38% in the control group. In treatment-experienced patients, 66% in the 48-week treatment group and 59% in the response-guided therapy group achieved SVR compared to 21% in the control group. Overall, 44% of patients in the SPRINT-2 response-guided treatment arm and 46% of patients in the RESPOND-2 response-guided treatment arm were eligible to undergo shortened treatment durations, based on cEVR results. Treatment discontinuations due to adverse events occurred in 12%-16% of treatment-naïve patients and 8%-12% of treatment-experienced patients, compared to 16% and 3% in the control groups, respectively (Fig. 2A/B).

**Other Protease Inhibitors**

A number of second-generation NS3/4A protease inhibitors are currently in early clinical development. Among these, danoprevir (RG7227), TMC435, vaniprevir (MK-7009), BI201335, narlaprevir (SCH900518), BMS-650032, PHX1766; ACH-1625, ABT-450, MK-5172, GS-9256, and GS-9451 have all been tested in phase 1 and/or phase 2 clinical trials [34-46]. Overall, these compounds exhibit a high antiviral activity in HCV genotype 1 patients and recently reported phase 2 results were comparable to, or even surpassed SVR results obtained with telaprevir and boceprevir [34, 39, 44].

Potential advantages of these second-generation protease inhibitors include improved pharmacokinetics (one to two times daily dosing), broader genotypic activity, coverage of first generation protease inhibitor resistance mutations and better tolerability. In addition, ritonavir boosting is being investigated in a number of protease inhibitors, including narlaprevir and danoprevir, to reduce side effects and to enhance patient exposure to the latter agents, thereby potentially overcoming resistance issues and allowing less frequent dosing.

Overlapping resistance profiles have been reported for all NS3 protease inhibitors that are currently in phase 2-3 development [47].

**Antivirals Targeting the HCV RNA Polymerase**

**NS5B Polymerase Inhibitors**

The active site of the HCV NS5B polymerase represents an interesting target for anti-HCV therapies as it forms a highly conserved structure across all HCV genotypes [48]. Currently, two classes of NS5B polymerase inhibitors can be distinguished - nucleoside or nucleotide analogue inhibitors that mimic the natural substrates of the RNA-dependent RNA-polymerase and are incorporated at the active site of the enzyme into the elongated RNA where they act as chain terminators, and non-nucleoside analogue inhibitors, representing a heterogeneous group of antiviral compounds that bind to different allosteric enzyme sites, resulting in a conformational protein change before the elongation complex is formed (Table 1).

**Nucleos(t)ide Inhibitors**

Nucleos(t)ide polymerase inhibitors target the active binding site of NS5B, with potential activity against all HCV genotypes. Despite promising results from early clinical studies, further development of the first two nucleoside polymerase inhibitors, valopicitabine and R1626, was halted due insufficient antiviral activity and severe adverse events [49-51].

RG7128, a prodrug of the cytidine nucleoside analogue PSI-6130, is currently under investigation in an
ongoing placebo-controlled phase 2b study in treatment-naïve patients with HCV genotype 1 or 4 (n=408). Interim results on complete early virologic response (cEVR; negative HCv RNA at week 12) showed up to 87% HCv RNA negativity for patients who received RG7128 at a dose of 1000 mg twice daily for 12 weeks plus SOC and no resistance related viral breakthrough was reported [52].

PSI-7977, a chirally pure isomer form of PSI-7851, has yielded promising early data with high RVR rates (88-94%) across different dose groups plus SOC in treatment-naïve patients with HCV genotype 1 [53]. The nucleotide analogue PSI-938 is still in the early stages of clinical development [54].

Non-nucleoside Inhibitors

The structure of the NS5B polymerase resembles a characteristic “right hand motif”, consisting of finger, palm and thumb domains. At least 4 different allosteric binding sites have been identified for the inhibition of the NS5B polymerase by non-nucleoside inhibitors - (i) a benzimidazole (thumb 1)-, (ii) a thiophene (thumb 2)-, (iii) a benzothiadiazine (palm 1)-, and (iv) a benzofuran (palm 2)-binding site [47]. As non-nucleoside inhibitors bind more distantly to the active site of NS5B, resistant mutations occur more frequently in these compounds.

(i) Non-nucleoside site 1 inhibitors

(thumb 1 / benzimidazole site)

BI 207127, BIL1941, and MK-3281 are non-nucleoside-site 1 inhibitors that have been shown to exhibit low to medium antiviral activity in phase 1 clinical trials [55-57]. Four weeks of BI 207127 (600 mg three times daily) in combination with PEG-IFN alfa-2a/RBV has resulted in a median reduction of 5.6 log10 HCv RNA in treatment-naïve genotype 1 patients and no viral breakthrough was observed [58]. Results of further studies have to be awaited. The further development of BIL1941 and MK-3281 was halted due to gastrointestinal adverse events.

(ii) Non-nucleoside site 2 inhibitors

(thumb 2 / thiophene site)

Interim results from a phase 1 trial investigating different doses of filibuvir (PF-00868554), a non-nucleoside site 2 inhibitor, in combination with SOC for 4 weeks followed by SOC for 44 weeks have shown similar SVR (at 12 weeks follow-up) results for the different filibuvir groups compared to the SOC group, indicating that longer dosing of filibuvir may be necessary [59]. Other site 2-inhibitors include VX-759, VX-916, and VX-222 [60-62]. However, at this point, only VX-222 has progressed to phase 2 developments.

(iii) Non-nucleoside site 3 inhibitors

(palm 1 / benzothiadiazine site)

A phase 2 trial of ANA598 in combination with PEG-IFN alfa-2a/RBV in treatment-naïve patients with HCV genotype 1 is currently ongoing. It was recently reported that 75% of patients who received 400 mg of ANA598 twice daily achieved undetectable HCv RNA levels at treatment week 12 [63]. Other site 3-palm 1-inhibitors include ABT-072 and ABT-333, both of which have entered phase 2 clinical trials [64].

(iv) Non-nucleoside site 4 inhibitors

(palm 2 / benzofuran site)

Monotherapy with HCV-796 (nexituvir) showed low antiviral activity in patients with HCV genotype 1. In addition, selection of resistant variants and viral breakthrough was observed in several patients [65]. Further drug development was suspended due to abnormal liver enzyme elevations in a subsequent phase 2 study. GS-9190 (tegobuvir) displayed low antiviral activity in a phase 1 clinical study and drug-resistant variants were observed. However, GS-9190 has entered phase 2 clinical trials, both in combination with SOC and with the protease inhibitor GS-9256 ± RBV [66]. Finally, IDX375 also binds to the palm pocket and is currently in phase 1 clinical trials [67].

NS5A Inhibitors

Inhibitors of NS5A are potentially active against all HCV genotypes. BMS-790052 binds to domain 1 of the NS5A protein, which is crucial for the regulation of HCv replication, assembly and release. Following the promising results from a phase 1 study [68], BMS-790052 is currently under investigation in a number of phase 2 clinical trials. Recently, interim data were released from a phase 2 study investigating different doses of BMS-790052 in combination with SOC. RVR rates were 83% and 92% in patients who received 10 mg and 60 mg BMS-790052 once daily, respectively. In addition, undetectable HCv RNA levels at week 12 (cEVR) were observed in 83% of patients [69]. Other NS5A inhibitors include BMS-824393, AZD7295, and PPI-461 [70-72].

DAA Combination Therapies

Treatment discontinuation rates due to interferon-associated side effects are commonly observed, especially in the routine daily practice [73]. Therefore, one of the primary future goals of DAA therapy is to control viral replication or even to achieve SVR in interferon-free regimens. In the placebo-controlled INFORM-1 study, combinations of different doses of a polymerase inhibitor (RG7128) and a NS3/4A protease inhibitor (danoprevir) were tested in 87 treatment-naïve and -experienced patients with HCv genotype 1 for up to 2 weeks [74]. At the highest doses tested (1000 mg RG7128 and 900 mg danoprevir twice daily), 63% of treatment-naïve patients and 25% of treatment-experienced patients achieved undetectable HCv RNA after 2 weeks of combination therapy and only one patient experienced viral rebound without exhibiting resistant mutations.

Several other drug combinations are actively being investigated. In a phase 2 study of the NS3 protease inhibitor GS-9256 (75 mg twice daily) plus the non-nucleoside NS5B polymerase inhibitor tegobuvir (40 mg twice daily) alone or in combination with RBV or PEG-IFN alfa/RBV for up to 28 days, viral breakthrough was observed for the combination of the two direct antiviral compounds only. This clearly shows
that two drugs with a low barrier to resistance are insufficient for continuous suppression of virus replication. Interestingly, the addition of RBV enhanced antiviral activity and reduced viral breakthrough rates, even in the absence of PEG-IFN alfa [75].

An IFN-sparing triple combination therapy with the NS3 protease inhibitor BI 201335 (12mg once daily) and the non-nucleoside polymerase inhibitor BI 207127 (400 mg or 600 mg three times daily) plus RBV resulted in residual or even undetectable HCV RNA levels after 4 weeks in all patients treated with the higher dose of BI 207127 [76].

Finally, in an ongoing trial of HCV genotype 1 null-responders treated with the NS5A inhibitor BMS-790052 plus the NS3 protease inhibitor BMS-650032 alone or in combination with PEG-IFN alfa/RBV for 24 weeks, 5/11 and 9/10 patients achieved cEVR, respectively. All patients with viral breakthrough in the DAA-only combination regimen (6/11) were genotype 1a patients. This important observation indicates that different antiviral activities of DAAs may be present on the HCV subtype level [77]. An overview of current combination therapy trials is given in Table 2.

Overcoming drug resistance will be the primary challenge in the DAA combination therapies and nucleos(t)ide analogues with a high genetic barrier to resistance and/or drug combinations that have a genetic barrier of four or more mutations may be required [78] (see Table 3). Future trials need to address the tolerability and safety of long-term DAA administration and whether SVR can be achieved without the addition of PEG-IFN alfa/RBV.

EMERGING MECHANISMS
Cyclophilin Inhibitors

Cyclophilins are ubiquitous proteins in human cells that are involved in protein folding. Moreover, cyclophilins participate in HCV replication as functional regulators of the HCV NS5B polymerase.

The cyclophilin inhibitor Debio-025 (alisporivir), a cyclosporine A analogue, showed antiviral activity in patients infected with different HCV genotypes (1–4) during monotherapy and in combination studies with PEG-IFN alfa. Maximum log_{10} changes in HCV RNA of up to 4.75 were observed in patients with HCV genotypes 1 or 4 who received 1000 mg Debio-025 in combination with PEG-IFN alfa-2a/RBV for 4 weeks [79]. Interestingly, there is even one case report of a genotype 3a patient who achieved SVR following 4 weeks of Debio-025 1000 mg/day as monotherapy [80]. Despite the selection of HCV variants with mutations clustering in the NS5A gene that showed resistance to Debio-025 in the HCV replicon system [81], no viral breakthrough has been observed in clinical studies so far.

SCY-635 is another non-immunosuppressive analogue of cyclosporine A that exhibits potent suppression of HCV. Different doses of SCY-635 were investigated in patients infected with HCV genotype 1 and a mean maximum decline of 2.3 log_{10} IU/ml in viral load was observed after 15 days of 900 mg SCY-635 monotherapy [82]. No viral rebound was observed during SCY-635 therapy. However, minimal evidence of resistance selection was observed within NS5B [83].

SILIBININ
Silymarin, an extract of milk thistle (Silybum marianum) with antioxidant activity has been used as self-medication for liver diseases over centuries [84]. Silibinin is one of the six major flavonolignans in silymarin. Though its mechanism of action and treatment efficacy is not yet fully understood, it was recently reported that silibinin is a direct inhibitor of the NS5B polymerase [85]. Other findings suggest that silymarin blocks virus entry and transmission, possibly by targeting the host cell [86].

Intravenous silibinin was investigated in 36 non-responders to prior PEG-IFN-based antiviral therapy and showed a significant decline in HCV RNA (0.55 to 3.02 log_{10} IU/ml) after 7 days and a further decrease after additional 7 days in combination with PEG-IFN alfa-2a/RBV in the range of 1.63 to 4.85 log_{10} IU/ml. HCV RNA became undetectable in 7 patients on 15 or 20 mg/kg silibinin at week 12 of total treatment [87]. Recently, it was reported that a short course of intravenous silibinin (2 days of 1400mg) could be used as a rescue approach in patients showing non-response to SOC [88]. Studies in larger patient cohorts including resistance analyses are underway.

NEW FORMULATIONS OF CURRENT THERAPIES
RIBAVIRIN ANALOGUES

Adverse haematological effects associated with RBV are commonly observed and have prompted the development of taribavirin, a prodrug that is converted to RBV and is concentrated in the liver, leading to reduced RBV uptake by red blood cells. In two phase 3 trials, administration of taribavirin (600 mg twice daily) plus PEG-IFN alfa-2a or -2b failed to achieve non-inferiority to administration of weight-based RBV plus PEG-IFN alfa-2a/b [89, 90]. In a recently completed phase 2b trial, weight-based taribavirin was non-inferior compared to weight-based RBV, with fewer haematological side effects [91]. However, anaemia rates increased with higher taribavirin dosing and the dropout rates for anaemia did not differ between the two study drugs. Therefore, the future role of taribavirin remains to be elucidated.

NEW INTERFERONS

Albinterferon alfa-2b (Joulferon) is a recombinant protein consisting of interferon alfa-2b fused to human albumin that can be administered every two or four weeks due to a longer half-life compared to the currently marketed pegylated interferons. However, albinterferon was neither better tolerated nor did it show superior efficacy in patients with HCV genotype 1 or 2/3 in two large phase 3 studies [92, 93]. Owing to concerns expressed by the regulatory authorities regarding the drug’s benefit/risk ratio, the approval process of albinterferon was recently suspended.
Table 2. Overview of current DAA combination therapies (ongoing and recently completed trials) with or without PEG-IFN/RBV in clinical development.

| Company          | NS3 Protease Inh. | NS5A Inh. | NS5B Nuc. Inh. | NS5B Non-Nuc. Inh. | Duration of DAA therapy | DAA alone | DAAs+ RBV | DAAs+ IFN/RBV | Prior treatment | Comments                                      |
|------------------|------------------|-----------|----------------|------------------|-------------------------|-----------|-----------|--------------|----------------|-----------------------------------------------|
| Roche            | Danoprevir*      | RG 7128   | (100mg TID)    | (500mg or 1000mg BID) | 1-2 weeks               | ✓         | ✓         |              | Naïve + Experienced | Proof-of-concept study; no resistance-emergence |
| Vertex           | Telaprevir       | VX-222    | (100mg or 400mg BID) | 12 weeks          | ✓ ✓                     | ✓         | ✓         |              | No             | No published results                            |
| Bristol-Myers    | BMS-650032       | BMS-790052 | (600mg BID)    | 24 weeks          | ✓ ✓                     | ✓         | ✓         |              | Prior null-responders only | Frequent virologic breakthrough in GT1a patients in DAA-only-study arm during first 12 weeks |
| Boehringer Ingelheim | BI 201335     | BI 207127 | (400mg or 600mg TID) | 4 weeks          | ✓ ✓ ✓                   | ✓         | ✓         |              | No             | 100% RVR in patients treated with the higher dose of BI 207127/RBV |
| Gilead           | GS-9256          | Tegobuvir | (40mg BID)     | 4 weeks          | ✓ ✓ ✓                   | ✓         | ✓         |              | No             | RBV delayed/reduced virologic breakthrough     |
| Abbott           | ABT-450/r        | ABT-072   | (40mg BID)     | 12 weeks          | ✓ ✓ ✓                   | ✓         | ✓         |              | No             | No published results                            |
| Pharmasset       | PSI-7977         | PSI-938   |                | 1-2 weeks         | ✓ ✓ ✓                   | ✓         | ✓         |              | No             | No published results                            |
| Idenix**         | IDX320           | IDX184    |                |                  |                         |           |           |              |                |                                               |

*Following significant liver enzyme elevations during a phase 2 study of danoprevir (900mg BID), subsequent DAA combination therapies are conducted with ritonavir-boosted danoprevir only; **this study has been placed on hold.

Table 3. Efficacy of different classes of anti-HCV agents with respect to resistance profile, genotype coverage and antiviral activity.

| NS3 Protease Inhibitors | NS5A Inhibitors | NS5B Nuc. Inhibitors | NS5B Non-Nuc. Inhibitors | Cyclophilin Inhibitors | PEG-Interferon alfa |
|------------------------|-----------------|----------------------|-------------------------|-----------------------|---------------------|
| Barrier to resistance  | low             | low                  | high                    | low                   | high                | very high           |
| Genotype coverage      | +               | +                    | +++                     | -                     | +                   | ++                  |
| Antiviral activity     | +++             | +++                  | ++                      | +                     | +/++                | +                   |
Locateron is a controlled release formulation of interferon alfa-2b that can be administered every two weeks. Week 12 interim results from a phase 2b study have shown a similar reduction in HCV RNA and a reduction of flu-like symptoms by 57% for loceteron at a dose of 480 µg compared to PEG-IFN alfa-2b in treatment-naive patient with HCV genotype 1 [94]. SVR results have now yet been reported.

A non-pegylated, type I interferon alpha-formulation, consensus interferon, has recently been approved in combination with ribavirin for non-responders to PEG-IFN therapy [95]. Finally, PEG-IFN lambda (PEG-rIL-29) is a type III interferon that binds to a unique receptor with more limited distribution than the type I interferon receptor used by interferon alpha. In a phase 1b trial, 56 treatment-naïve patients and patients who relapsed after SOC were enrolled to receive different doses of PEG-IFN lambda (ranging from 0.5 to 3.0 µg/kg) administered every two weeks or weekly with or without daily RBV for four weeks. Antiviral activity was seen at all dose levels with a mean maximum change of HCV RNA from baseline of 3.27 log_{10} IU/ml in treatment naïve patients treated with weekly PEG-IFN lambda (1.5µg/kg) plus RBV [96]. In addition, minimal flu-like symptoms and no significant hematological side effects were observed. Phase 2 trials are currently ongoing.

**Conclusions**

While treatment success in patients with HCV genotype 1, the most prevalent genotype in Europe and the USA, remains suboptimal with the current standard of care, a number of promising direct-acting antiviral compounds offer new hope for a cure.

Recently completed pivotal phase 3 studies of the currently most advanced NS3/4A protease inhibitors, telaprevir and boceprevir, have shown SVR rates in the range of 69-75% and 63-66%, respectively, in treatment-naïve patients with HCV genotype 1 infection. Additional important findings include the successful application of shortened treatment durations of 24/28 weeks in 50-65% of patients, based on extended rapid on-treatment response. Finally, patients who failed a prior course of interferon-based therapy may also be successfully cured, with SVR rates of 64-66% and 59-66% in telaprevir- and boceprevir-based regimens, respectively. No protease inhibitor head-to-head studies have been conducted so far.

Nucleos(t)ide and non-nucleoside inhibitors of the HCV NS5B polymerase have shown promising antiviral efficacy in early clinical studies. Unlike protease inhibitors, which are mostly active in patients with HCV genotype 1 only, nucleos(t)ide polymerase inhibitors bind to the highly conserved centre of the HCV polymerase, with the potential advantage of equal effectiveness in different HCV genotypes. However, SVR results from larger studies have to be awaited.

At present, a number of studies focus on different combinations of different HCV protease and polymerase inhibitors with or without the addition of SOC. While a rapid and profound decline in HCV RNA was observed in most of these studies, sustained virologic response may be only achieved with combination therapies using at least 3 compounds or with PEG-IFN/RBV as a therapeutic backbone for the foreseeable future.

While HCV protease and polymerase inhibitors are likely to take the lead in future anti-HCV drug regimens, there are a number of additional therapeutic approaches that may eventually find their place within the HCV armamentarium. Among these, inhibitors of the non-structural protein 5A and cyclophilin inhibitors are currently the furthest along in the pipeline.

With the addition of new antiviral compounds to standard therapy, a number of additional side effects unrelated to SOC have been observed, and increased treatment-discontinuation rates have been reported. Consequently, successful management of these side effects will gain in importance and will have increasing influence on treatment outcomes. In addition, frequent dosing intervals (i.e. three times daily) may lead to increased non-adherence outside of clinical trials and more patient-friendly formulations have to be developed.

One of the major challenges of future anti-HCV treatment regimens will be the emerging field of DAA drug resistance. Relatively low genetic barriers to resistance have been reported for HCV protease inhibitors and non-nucleoside polymerase inhibitors as compared to nucleos(t)ide HCV polymerase inhibitors that appear to have a high genetic barrier to resistance. However, HCV eradication may not be achieved with monotherapy from either substance group and drug combinations with non-cross-resistance patterns have to be further evaluated. In addition, pre-existing resistant variants and their potential long-term persistence have to be taken into account for the selection of optimal treatment and re-treatment strategies. Finally, the potential risks of drug-drug interactions, especially in patients with HIV co-infection who are on antiretroviral therapy, will likely gain in importance, while numbers of patients treated with DAs are increasing. Therapeutic drug monitoring may eventually play an important role in the management of these interactions [97].

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