Review

The science of direct-acting antiviral and host-targeted agent therapy

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Introduction

In principle, every step of the HCV life cycle, including receptor binding, endocytosis, fusion, uncoating, translation, polyprotein processing, RNA replication, virion assembly, maturation, transport and release, can be a target for new anti-HCV drugs [1]. Thus far, direct-acting antiviral (DAA) drugs targeting two major steps of the HCV life cycle have reached clinical development. They include inhibitors of the HCV NS3-4A protease that block polyprotein processing and several drug families that block viral replication, including nucleoside/nucleotide inhibitors of the HCV-RNA-dependent RNA polymerase (RdRp), non-nucleoside inhibitors of the HCV RdRp, and inhibitors of the NS5A viral protein which plays a regulatory role in replication [1,2]. Host-targeted agents (HTAs) include drugs that inhibit the host cell protein cyclophilin A, a protein required to interact with the replication complex for efficient viral genome production [1,2], and an antagonist of microRNA-122 [3].

The HCV life cycle, a target for DAAs and HTAs

The multiple steps of the HCV life cycle offer a very large number of potential targets of intervention for specific anti-HCV drugs, including DAAs and HTAs. Viral attachment, entry and fusion

HCV displays two glycoproteins, E1 and E2, at its surface. The latter is involved in receptor binding at the surface of target cells. Several cell-surface molecules mediate HCV binding and internalization, including glycosaminoglycans and the low-density lipoprotein receptor, which could serve as the initial docking site for HCV attachment [4–7]; the tetraspanin CD81, which could act as a post-attachment entry co-receptor [8,9]; the scavenger receptor B1, an essential component of the cellular HCV receptor complex [10–12]; claudin-1 and occludin, which appear to act late in the entry process, after the interaction with CD81 [13,14]. After attachment, HCV entry into cells has been shown to be pH-dependent and related to clathrin-mediated endocytosis. Entry is followed by a fusion step within an acidic endosomal compartment. The identity of the HCV fusion peptide remains controversial. Recently, epidermal growth factor receptor and ephrin receptor A2, two receptor tyrosine kinases, were shown to play an important role in HCV entry by regulating CD81–claudin-1 co-receptor associations and viral glycoprotein-dependent membrane fusion [15]. Niemann-Pick C1-like 1 cholesterol absorption receptor was also identified as an HCV cell entry factor that functions after binding, at or before fusion [16].
RNA translation
Decapsidation of viral nucleocapsids liberates free positive-strand genomic RNAs in the cell cytoplasm, where they serve, together with newly synthesized RNAs, as messenger RNAs for synthesis of the HCV polyprotein. The HCV 5′ untranslated region (5′UTR), the most conserved region of the HCV genome, contains several domains that are highly structured in numerous stem-loops and a pseudoknot, and constitute, together with the first 12 to 30 nucleotides of the core-coding region, the internal ribosome entry site (IRES), which controls HCV genome translation [17]. The IRES mediates cap-independent internal initiation of HCV polyprotein translation by recruiting both cellular proteins, including eukaryotic initiation factors 2 and 3, and viral proteins.

Polyprotein processing
The large precursor polyprotein generated by HCV genome translation is targeted to the endoplasmic reticulum membrane where the processing events take place. The co- and post-translational processing of the HCV polyprotein results in the generation of at least 11 proteins, including 3 structural proteins (C or core, E1 and E2), a viroporin, p7, 6 non-structural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B), and the so-called ‘F’ protein that results from a frameshift in the core-coding region [18]. At least two host cellular peptidases are required for processing of the HCV structural proteins, including host signal peptidase and signal peptide peptidase. Two viral peptidases are involved in the processing of HCV NS proteins: NS2, a zinc-dependent metalloproteinase that cleaves the site between NS2 and NS3; and NS3/4A, a serine proteinase that catalyses HCV polyprotein cleavage at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B junctions. The viral proteins remain associated with intracellular membranes after processing [18].

Replication
Replication is catalysed by the HCV RdRp or NS5B protein. The NS5A protein plays an important regulatory role in virus replication, but the mechanisms are still uncertain. The NS3 helicase-NTPase domain of the NS3 protein has several functions important in replication, including RNA-stimulated NTPase activity, RNA binding, and unwinding of RNA regions of extensive secondary structure [19,20]. Finally, NS4B is an integral membrane protein which serves as a membrane anchor for the replication complex and plays an important role in membrane rearrangements leading to the formation of the ‘membranous web’ or replication complex that supports and compartmentalizes HCV replication [18,21–23].

The replication complex associates viral proteins, cellular components and nascent RNA strands. By analogy with other positive-strand RNA viruses, it is believed that the positive-strand genome RNA serves as a template for the synthesis of a negative-strand intermediate of replication. Then, negative-strand RNA serves as a template to produce numerous strands of positive polarity that will subsequently be used for polyprotein translation, synthesis of new intermediates of replication or packaging into new virus particles [18,24]. A number of host cellular factors are involved in HCV replication, such as cyclolin A, a peptidy-prolyl cis/trans isomerase required for HCV replication through its interaction with NS5A and the RdRp at the replication complex level, microRNA-122, which augments HCV replication through its binding at two specific sites within the 5′UTR of the HCV genome, or phosphatidylinositol-4 kinase III-α, which plays an important role in replication complex formation. Like viral functions, host-cell factors represent potential targets for anti-HCV therapies [25].

Assembly and release
Viral particle formation is probably initiated by the interaction of the core protein with genomic RNA [26,27]. HCV uses the lipoprotein production pathway to generate mature viral particles and export them. Cytoplasmic lipid droplets serve as virus assembly platforms and several NS proteins appear to play a role in the late steps of the HCV life cycle, including p7, NS2, NS3 and NS5A. The very low-density lipoprotein synthesis/secretion machinery appears to be involved in infectious HCV production [28]. The mechanisms underlying exportation of mature virions in the pericellular space or their transfer to neighbouring cells have yet to be understood.

DAAs and HTAs in clinical development
Virtually every step of the HCV life cycle can be the target for one or several families of drugs that block virus production. As a result, a number of HCV DAAs and HTAs are at the developmental stage. Nevertheless, only molecules that target polyprotein processing (that is, NS3-4A protease inhibitors) and inhibitors of HCV replication through various targets and mechanisms have reached clinical development. The latter include nucleoside/nucleotide analogue inhibitors of HCV RdRp, non-nucleoside inhibitors of RdRp, NS5A inhibitors, cyclophilin inhibitors and a microRNA-122 antagonist.

NS3-4A protease inhibitors
A large number of NS3-4A protease inhibitors have reached clinical development, including two drugs, telaprevir and boceprevir, that have been recently approved for use in combination with pegylated interferon (IFN)-α and ribavirin in patients infected with
HCV genotype 1 [29–32]. NS3-4A protease inhibitors have closely related chemical structures. They are peptidomimetic compounds that target the catalytic site of the enzyme and block post-translational processing of the viral protein that gives birth to NS proteins NS4A, NS4B, NS5A and NS5B. NS3-4A protease inhibitors inhibit viral replication by 3.5 to 4.5 log IU/ml when administered alone for a few days (Table 1) [33–42]. Telaprevir and boceprevir are active against genotypes 1 and 2 only, whereas other protease inhibitors have

Table 1. DAAs and HTAs in clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Phase</th>
<th>Dose</th>
<th>Duration</th>
<th>Mean/median log HCV RNA reduction, IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS3–4A protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Vertex &amp; Janssen</td>
<td>Approved</td>
<td>750 mg every 8 h</td>
<td>14 days</td>
<td>-4.4</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Merck</td>
<td>Approved</td>
<td>400 mg three times a day</td>
<td>7 days</td>
<td>-1.6</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Janssen</td>
<td>III</td>
<td>200 mg daily</td>
<td>7 days</td>
<td>-4.1</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>Boehringer Ingelheim</td>
<td>III</td>
<td>240 mg daily</td>
<td>14 days</td>
<td>-4.0</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>Roche/Genentech</td>
<td>II</td>
<td>200 mg every 8 h</td>
<td>14 days</td>
<td>-3.8</td>
</tr>
<tr>
<td>Vaniprevir</td>
<td>Merck</td>
<td>II</td>
<td>700 mg twice a day</td>
<td>8 days</td>
<td>-4.7</td>
</tr>
<tr>
<td>Narlaprevir/f</td>
<td>Merck</td>
<td>II</td>
<td>400 mg twice a day</td>
<td>7 days</td>
<td>-4.2</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>Bristol–Myers Squibb</td>
<td>II</td>
<td>300 mg twice a day</td>
<td>3 days</td>
<td>-3.3</td>
</tr>
<tr>
<td>GS-9256</td>
<td>Gilead</td>
<td>II</td>
<td>450 mg daily</td>
<td>1 day</td>
<td>-2.7</td>
</tr>
<tr>
<td>GS-9451</td>
<td>Gilead</td>
<td>II</td>
<td>400 mg daily</td>
<td>3 days</td>
<td>-3.5</td>
</tr>
<tr>
<td>ABT-450/f</td>
<td>Abbott</td>
<td>II</td>
<td>200 mg daily</td>
<td>3 days</td>
<td>-4.1</td>
</tr>
<tr>
<td>ACH-1625</td>
<td>Achillion</td>
<td>II</td>
<td>600 mg daily</td>
<td>5 days</td>
<td>-4.2</td>
</tr>
<tr>
<td>MK-5172</td>
<td>Merck</td>
<td>II</td>
<td>400 mg daily</td>
<td>7 days</td>
<td>-5.4</td>
</tr>
<tr>
<td><strong>Nucleoside/nucleotide analogue inhibitors of HCV RNA-dependent RNA polymerase</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GS-7977</td>
<td>Gilead</td>
<td>III</td>
<td>400 mg daily</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
<tr>
<td>Mericitabine</td>
<td>Roche/Genentech</td>
<td>II</td>
<td>1,500 mg twice a day</td>
<td>14 days</td>
<td>-2.7</td>
</tr>
<tr>
<td>IDX184</td>
<td>Idenix</td>
<td>II</td>
<td>100 mg daily</td>
<td>3 days</td>
<td>-0.7</td>
</tr>
<tr>
<td>INX-189</td>
<td>Bristol–Myers Squibb</td>
<td>II</td>
<td>100 mg daily</td>
<td>7 days</td>
<td>-2.5</td>
</tr>
<tr>
<td><strong>Non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegobuvir</td>
<td>Gilead</td>
<td>II</td>
<td>40 mg twice a day</td>
<td>8 days</td>
<td>-1.4</td>
</tr>
<tr>
<td>Filibuvir</td>
<td>Pfizer</td>
<td>II</td>
<td>300 mg twice a day</td>
<td>8 days</td>
<td>-2.1</td>
</tr>
<tr>
<td>Sotrobuvir</td>
<td>Roche/Genentech</td>
<td>II</td>
<td>800 mg twice a day</td>
<td>3 days</td>
<td>-2.9</td>
</tr>
<tr>
<td>BI207127</td>
<td>Boehringer Ingelheim</td>
<td>II</td>
<td>800 mg every 8 h</td>
<td>3 days</td>
<td>-3.1</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott</td>
<td>II</td>
<td>600 mg twice a day</td>
<td>2 days</td>
<td>-1.5</td>
</tr>
<tr>
<td>VX-222</td>
<td>Vertex</td>
<td>II</td>
<td>750 mg twice a day</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
<tr>
<td><strong>NS5A inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Bristol–Myers Squibb</td>
<td>II</td>
<td>10 mg daily</td>
<td>1 day</td>
<td>-3.2</td>
</tr>
<tr>
<td>PPI-461</td>
<td>Presidio</td>
<td>II</td>
<td>100 mg daily</td>
<td>3 days</td>
<td>-3.7</td>
</tr>
<tr>
<td>GS-5885</td>
<td>Gilead</td>
<td>II</td>
<td>30 mg daily</td>
<td>3 days</td>
<td>-3.3</td>
</tr>
<tr>
<td>BMS-824393</td>
<td>Bristol–Myers Squibb</td>
<td>II</td>
<td>50 mg daily</td>
<td>3 days</td>
<td>-3.9</td>
</tr>
<tr>
<td><strong>Cyclophilin inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alisporivir</td>
<td>Novartis</td>
<td>III</td>
<td>1,200 mg twice a day</td>
<td>14 days</td>
<td>-3.6</td>
</tr>
<tr>
<td>SCY-465</td>
<td>Scynexis</td>
<td>II</td>
<td>900 mg daily</td>
<td>15 days</td>
<td>-2.2</td>
</tr>
<tr>
<td><strong>microRNA–122 antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miravirsen</td>
<td>Santaris</td>
<td>lb</td>
<td>7 mg/kg/week</td>
<td>4 weeks</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

The table shows the mean or median HCV RNA level reduction in Phase Ib trials. The dosages in these trials could be different from those in subsequent Phase II or III clinical trials. Durations of administration differed between the different drugs. DAA, direct-acting antiviral; HTA, host-targeted agents.
broader genotype coverage; however, none of the first-generation NS3-4A protease inhibitors is fully active against genotype 3 (except, maybe, boceprevir that has been reported to reduce HCV RNA levels by 1.7 log IU/ml in 4 patients infected with HCV genotype 3 [43]). With some protease inhibitors, dosing intervals have been extended while enhancing patient exposure and reducing side effects by means of ritonavir boosting (100 mg/day) [33,41,44].

First-generation protease inhibitors have a low barrier to resistance. Indeed, a large number of amino acid substitutions conferring resistance to protease inhibitors have been shown to pre-exist at generally low levels in infected patients and are selected within a few days to weeks on drug monotherapy [45–47]. Different resistance profiles have been reported for subtypes 1a and 1b. The profiles also slightly differ between different members of the family. However, cross-resistance is conferred by most of these amino acid substitutions.

Second-generation NS3-4A protease inhibitors, such as for instance MK-5172, have pangenotypic coverage (including genotype 3) and a higher barrier to resistance [48].

Nucleoside/nucleotide analogue inhibitors of HCV RdRp
Nucleoside/nucleotide analogues target HCV RNA formation within the catalytic site of the HCV RdRp. They act as false substrates for the RdRp, leading to chain termination after incorporation into the newly synthesized RNA chain. Nucleoside analogues need three phosphorylation steps to be activated. In contrast, nucleotide analogues are already phosphorylated and need only two additional phosphorylations, making them more rapidly active at the target site. Several drugs have reached clinical development, including purine and pyrimidine analogues (Table 1) [49,50]. They are active on all known genotypes and subtypes. One single amino acid substitution is sufficient to confer resistance to C-methyl nucleosides. However, due to the mutational bias of HCV RdRp in favour of transitions over transversions [51], this mutation is less likely to occur than mutations conferring resistance to other drug families. In addition, variants bearing this amino acid substitution exhibit extremely low fitness and are thus unlikely to grow and fill in the replication space and subsequently become clinically meaningful. Therefore, nucleoside/nucleotide analogues have a high ‘barrier’ to resistance.

Non-nucleoside inhibitors of HCV RdRp
Non-nucleoside inhibitors of HCV RdRp are a heterogeneous group of drug families targeting one of four allosteric sites at the surface of the viral enzyme, including ‘thumb’ domains I and II and ‘palm’ domains I and II (Table 1) [52–57]. Their binding alters the three-dimensional structure of the RdRp, thereby altering its catalytic function and blocking RNA replication. Their antiviral action is thus far restricted to HCV genotype 1 in most instances. Different non-nucleoside inhibitors have different antiviral potencies (Table 1) [52–57]. They select amino acid substitutions conferring resistance that are generally, but not always, located in close vicinity to their target site. They have a low genetic barrier to resistance, and selected variants are generally fit. Extensive cross-resistance has been reported between drugs targeting the same site, and cross-resistance can also occur between drugs targeting different sites.

NS5A inhibitors
NS5A inhibitors bind to domain I of the NS5A protein and block its ability to regulate HCV replication within the replication complex, through an as-yet-unclear mechanism. They could inhibit both the cis and trans functions of NS5A and perturb the function of newly formed replication complexes through redistribution of this viral protein from the endoplasmic reticulum to lipid droplets [58,59]. NS5A inhibitors are potent and have pangenotypic coverage, but the barrier to resistance of first-generation molecules is low for HCV subtype 1a (Table 1) [60–64].

Cyclophilin inhibitors
Cyclophilin A plays an important role in the HCV replication cycle by binding to both NS5A and the RdRp within the viral replication complex. Blocking its peptidyl-prolyl cis-trans isomerase enzyme activity is associated with a significant inhibition of HCV replication, through mechanisms that remain unclear [65]. Because their target is a host protein (HTAs), cyclophilin inhibitors have pangenotypic coverage and a high barrier to resistance [66]. Variants bearing amino acid substitutions in the NS5A protein have been selected after numerous passages in cell culture. However, these substitutions confer low-level resistance and the corresponding variants exhibit low fitness both in vitro and in vivo.

Other HTAs
A number of HTAs are also reaching the clinical developmental stage, including, for instance, an HCV entry inhibitor that targets scavenger receptor B-1 or a microRNA-122 antagonist that inhibits HCV replication.

Mechanisms of therapeutic HCV clearance
In order to achieve a sustained virological response (SVR), which corresponds to a cure of the HCV infection, three steps are required [67]. It is necessary: first, to shut down virus production to achieve
a rapid initial reduction of circulating HCV RNA levels. IFN-α in IFN-responders, and both DAAs and HTAs have potent antiviral properties and are able to induce a steep first-phase decline in HCV RNA. Secondly, to maintain viral inhibition throughout treatment, that is, to prevent viral breakthrough due to the selection of resistant viral variants or to poor adherence to therapy. Thirdly, to induce a significant, slower second-phase decline in HCV RNA level, resulting of gradual clearance of HCV-infected liver cells through cell death or, more often, HCV removal from infected cells [68]. Restoration of the cellular innate immune response as a result of the inhibition of viral protein production plays an important role in the clearance of residual HCV genomes. An SVR can be achieved only if the second-phase decline is gradual and treatment is administered for a sufficient duration, ensuring that every infected cell has been cleared or cured when it is stopped; therefore, treatment duration is key to achieve an SVR. Ribavirin addition enhances the second-phase decline, accelerating the clearance of infected cells through unknown molecular mechanisms and allowing for shorter treatment duration [69–71].

Curing HCV infection with interferon-containing DAA and/or HTA regimens

Resistance to antiviral drugs is classically prevented by combining several drugs with potent antiviral activity and no cross-resistance [72]. Viral breakthrough due to HCV resistance to DAAs with a low barrier to resistance is significantly less frequent when one of these drugs is administered in combination with pegylated IFN-α or with both pegylated IFN-α and ribavirin [73–75]. The triple combination of pegylated IFN-α, ribavirin and a protease inhibitor, telaprevir or boceprevir, has now become the standard-of-care therapy for treatment-naive and treatment-experienced patients with HCV genotype 1 infection. A number of other triple or quadruple combinations of one or two DAA(s) and/or HTA(s), respectively, with pegylated IFN-α and ribavirin are currently being evaluated in clinical trials.

Triple-combination treatment regimens

In treatment-adherent patients, eradication of HCV infection with the triple combination of pegylated IFN-α, ribavirin and a protease inhibitor is frequent in good responders to IFN and ribavirin. Conversely, failure to eradicate HCV results primarily from an inadequate response to pegylated IFN-α and ribavirin, which leads to uncontrolled outgrowth of resistant variants selected by the protease inhibitor [29,31,32]. Indeed, in the clinical trials that included a ‘lead-in’ phase, consisting of pegylated IFN-α plus ribavirin for 4 weeks before adding the protease inhibitor, the probability of achieving an SVR during triple-combination therapy was of the order of 80% when the HCV RNA level had been reduced by more than 1.0 log₁₀ IU/ml, and of the order of 30% when it had been reduced by less than 1.0 log₁₀ IU/ml at week 4 of the lead-in phase, regardless of the total treatment duration [29,31,32]. Similar findings have been reported with other protease inhibitors and drugs belonging to other families in combination with pegylated IFN-α and ribavirin. It is too early to say whether the effect of IFN responsiveness on the outcome of triple-combination therapy will be attenuated when drugs with a high barrier to resistance are used in combination with pegylated IFN-α and ribavirin.

Quadruple-combination treatment regimens

Interest was recently raised about quadruple combination treatment regimens that combine pegylated IFN-α, ribavirin and two DAAs belonging to different drug classes without cross-resistance. In a study in patients who previously experienced a null response to pegylated IFN-α and ribavirin, 10 out of 10 patients receiving a quadruple-combination including an NS5A inhibitor and an NS3-4A protease inhibitor achieved an SVR [76]. The number of patients in this study was too small to reach firm conclusions and it also remains to be established whether two drugs with a low barrier to resistance do better in combination with pegylated IFN-α and ribavirin than one drug with a high barrier to resistance, or whether quadruple combinations may be further improved by including at least one drug with a high barrier to resistance.

Curing HCV infection with interferon-free DAAs and/or HTA regimens

As explained above, high SVR rates can be achieved with all-oral, IFN-free drug regimens only if the drug or drug combination is potent enough to efficiently shut down virus production, has a high enough barrier to resistance to maintain viral inhibition throughout treatment, and is able to induce a steep and consistent second-phase decline that will lead to the definitive clearance or cure of HCV-infected liver cells.

Antiviral effectiveness

The first-phase decline is rapid and profound with most available DAAs used as monotherapies. The antiviral effectiveness of the drugs presented in Table 1 is difficult to compare, because different dosages and durations have been applied. However, antiviral effectiveness of drugs from the four families of DAAs having reached clinical development can reach -3.0 to -4.0 log₁₀ IU/ml at day 3 in many instances (Table 1). Similar antiviral effectiveness can be achieved after more days of administration with drugs that need to be activated, such as mericitabine, a nucleoside analogue that requires to
be phosphorylated three times, or with HTAs, such as IFN-α or cyclophilin inhibitors.

Barrier to resistance

DAAs and HTAs are characterized by their barrier to resistance, which is influenced by three major related factors in vivo [77]. Firstly, the genetic barrier to resistance, which can be defined at several levels: the number of nucleotide substitutions needed to generate a resistant variant, which may vary according to the genotype or subtype for a given drug or class of drugs; the likelihood that a nucleotide mutation responsible for an amino acid change associated with resistance occurs, which is influenced by the mutational bias of HCV RdRp in favour of transitions over transversions [51]; the number of amino acid substitutions needed for a viral variant to acquire full resistance to the drug, which may also vary according to the genotype or subtype. Secondly, the in vivo fitness of the resistant viral population, defined as the ability of the variant to survive and grow in the replication environment in the presence of drug. Thirdly, drug exposure: resistant variants will be inhibited if the drug levels achieved in vivo are far above their 90% inhibitory concentration against these resistant variants.

HCV drugs in development can be split into two groups according to their barrier to resistance. HCV DAAs with a low barrier to resistance include first-generation NS3-4A protease inhibitors, non-nucleoside inhibitors of HCV RdRp and, for certain subtypes such as subtype 1a, first-generation NS5A inhibitors. HCV drugs with a high barrier to resistance include nucleoside/nucleotide analogues, possibly second-generation protease and NS5A inhibitors, and HTAs, such as cyclophilin inhibitors. The combination of two oral drugs with a low barrier to resistance was recently shown to result in early virological breakthroughs due to the selection of viral populations that were resistant to both drugs [76,78]. In contrast, the use of combinations including at least one drug with a high barrier to resistance, such as a nucleoside/nucleotide analogue regardless of the HCV genotype/subtype, or an NS5A inhibitor in patients infected with subtype 1b, was shown to reach a high barrier to resistance [79–81].

Infected cell clearance

The second-phase decline is the combined result of the natural death rate of infected cells and the rate of loss of the ability of the remaining infected cells to produce virus as their intracellular RNA degrades (cell cure) [68]. The second-phase decline is under the influence of several parameters, including antiviral treatment effectiveness, that is, the first-phase decline (a more potent blocking of virus production is associated with a steeper second-phase decline) [82]; the genetic background of the host (the IL28B genotype was recently shown to influence the second-phase slope without altering the initial antiviral response to a combination of DAAs) [83]; the severity of liver disease (fibrosis and cirrhosis are associated with a slower clearance of infected cells, through mechanisms that remain to be elucidated). Therefore, the duration of treatment required to eradicate infection varies from one patient to another, and a fixed duration of treatment will not fit all patients. Further studies are needed to establish the appropriate treatment duration in different groups of patients receiving all-oral, IFN-free treatment regimens.

In combination with pegylated IFN-α, ribavirin has been shown to accelerate the second-phase decline and shorten the required treatment duration [69–71]. Recent findings suggest that this effect is not IFN-dependent and can be obtained when ribavirin is combined with potent DAAs [78,80]. Therefore, ribavirin addition is likely to be useful to shorten treatment duration with future all-oral, IFN-free regimens. The mechanisms by which ribavirin exerts its effects in HCV therapy remain debated [84]. They are not related to a direct antiviral effect.

Conclusion

Recent findings suggest that HCV infection is relatively easy to cure, provided that appropriate tools are used. The advent of new antiviral molecules, including DAAs and HTAs, has provided a proof-of-concept that HCV infection can be cured by all-oral IFN-free treatment regimens within 12 to 24 weeks and that very high SVR rates can be achieved with drugs or drug combinations that have a high barrier to resistance. They suggest that the IFN era is coming to an end in hepatitis C therapy, although this end cannot yet be precisely dated. Further results are awaited that will allow the establishment of an ideal first-line all-oral, IFN-free treatment regimen for patients with chronic HCV infection.

Disclosure statement

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References


