Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Perspectives and challenges of interferon-free therapy for chronic hepatitis C

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Summary

Recent data have clearly shown that a sustained virologic response can be achieved in different HCV infected patient populations with various interferon-free treatment regimens. Despite the successful implementation of telaprevir- and boceprevir-based triple therapies, all-oral regimens will certainly become a first choice for a number of HCV-infected patients in the very near future, as triple therapy approaches are burdened with significant side-effects and limited success in patients with advanced liver fibrosis and prior null-response to pegylated interferon-α (pegIFN-α)/ribavirin therapy. However, available data from phase I and II clinical trials evaluating interferon-free regimens have not yet revealed a clearly outstanding all-oral combination, and numerous challenges remain to be addressed by intensive ongoing and future research. In particular, thus far evaluated all-oral regimens did not cure a satisfactory percentage of patients with unfavorable baseline characteristics, namely patients infected with HCV genotype 1a, previous null-response to pegIFN-α/ribavirin, or liver cirrhosis. In this review, we summarize available data of interferon-free regimens for the treatment of chronic hepatitis C and assess implications for perspectives and challenges in the further development of all-oral therapies.

A need for interferon-free treatment regimens for chronic hepatitis C

The approval of the hepatitis C virus (HCV) protease inhibitors telaprevir and boceprevir in 2011 represents a major breakthrough in the treatment of chronic hepatitis C. For HCV genotype 1 patients, telaprevir- or boceprevir-based combination therapy with pegylated interferon-α (pegIFN-α) and ribavirin constitutes the novel standard of care, since significantly higher SVR rates compared to pegIFN-α and ribavirin alone have been demonstrated for both treatment-naïve and -experienced patients [1–4]. Nevertheless, telaprevir or boceprevir-based triple therapy has certain limitations. In particular, the interferon-sensitivity of individual patients remains a major determinant of treatment success because a slow decline of HCV viral load during triple therapy is associated with a high risk for the selection of resistance associated variants (RAVs) [5]. Consequently, viral breakthrough of drug resistant variants was observed in a significant number of patients with partial- or null-response to previous treatment with pegIFN-α and ribavirin, in patients with limited decline of HCV viral load during lead-in treatment with pegIFN-α and ribavirin alone, or in difficult-to-cure populations like African-Americans or patients with advanced liver fibrosis [1,4]. To overcome the risk of treatment failure in such patients, triple therapy regimens, including more potent directly acting antiviral agents (DAA), or quadruple therapies based on therapy of pegIFN-α and ribavirin plus combination of two DAAs derived from different molecular classes, may be applicable. A high potential of these approaches has already been demonstrated in phase I and II clinical trials, with outstanding SVR rates especially after quadruple therapy even in previous null responders to pegIFN-α and ribavirin alone [6,7]. However, these clinical trials were performed in highly selected patients, and both triple and quadruple therapy approaches are no option for patients with contraindications to pegIFN-α or ribavirin, such as patients with decompensated liver cirrhosis or liver transplant failure. This is especially relevant in view of the rising age of the HCV-infected population in the Western world, which implicates an increasing number of patients with advanced liver disease and previous treatment failure in the next decade [8]. Hence, a large count of patients with chronic hepatitis C not tolerating IFN-α but urgently requiring antiviral therapy can be anticipated in the near future. To be forearmed to this significant medical need – and to offer "easier-to-treat" patients, more convenient treatment modalities than IFN-α-based regimens – intensive research currently addresses the potential of interferon-free, all-oral DAA therapies. In this review, we summarize available safety and efficacy data of these interferon-free regimens and offer an assessment of future perspectives and limitations of all-oral therapies.

Keywords: Hepatitis C virus; Antiviral therapy; Directly acting antiviral agent; All-oral therapy; Null responder.
Received 29 August 2012; received in revised form 28 September 2012; accepted 13 October 2012
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Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response; RVR, rapid virologic response; eRVR, extended rapid virologic response; EVR, early virologic response; peg, pegylated; IFN, interferon; *IL28B*, interleukin 28B; DAA, directly acting antiviral agent.

Review

Key Points

- The increasing number of HCV-infected patients with advanced liver disease and patients with contraindications to interferon-based therapies represents an urgent medical need to develop potent interferon-free treatment regimens
- Currently available DAAs differ significantly in their antiviral efficacy, genetic barrier to resistance, and HCV genotype coverage. Novel nucleoside analogue NS5B inhibitors (NIs) are attractive candidates for the backbone of interferon-free regimens, as they display a high antiviral activity, together with broad genotypic coverage and a high barrier to resistance. NS3-4A inhibitors and NS5A inhibitors are also characterized by a profound antiviral potency, but their barrier to resistance is relatively low
- Various combinations of two or more DAAs with or without ribavirin led to SVR in different patient populations. Powerful interferon-free regimens - at least in patients with favorable baseline characteristics - included for example the combination of the NI sofosbuvir (GS-7977) with the NS5A inhibitor daclatasvir, or combinations of NS3-4A inhibitors with NS5A inhibitors, NIs or selected non-nucleoside NS5B inhibitors, + ribavirin
- The addition of ribavirin to all-oral regimens in general had an important impact on the prevention of viral breakthrough. In selected regimens with both a high genetic barrier to resistance and potent antiviral activity, the addition of ribavirin may be unnecessary
- Previous non-response to PegIFNα and ribavirin therapy, infection with HCV subtype 1a, poor compliance, and poor-response *IL28B* genotype are predictors of failure of interferon-free treatment regimens. However, the relevance of these negative predictors of treatment outcome differs significantly according to the potency of specific all-oral regimens
- A better characterization of HCV quasispecies at baseline and after failure of interferon-free regimens is necessary to clarify the impact of resistance-associated variants (RAVs) on outcome and choice of specific all-oral regimens
- A case of late relapse between week 24 and 36 after completion of treatment with ABT-450/r, ABT-072, and ribavirin may indicate a need for longer follow-up times than SVR_{24} after treatment with all-oral regimens

The current repertoire of DAA agents for all-oral combination therapies

HCV NS3-4A protease inhibitors

NS3-4A inhibitors target the shallow enzymatic groove of the HCV protease and thereby inhibit HCV polyprotein procession, a crucial step in the early HCV life cycle [9]. In the meanwhile, numerous NS3-4A protease inhibitors have been developed which can be divided into two molecular classes, the macrocyclic inhibitors and linear tetra-peptide α-ketoamide derivatives [9] (Table 1). In general, NS3-4A inhibitors are characterized by a remarkable antiviral activity, but also by a low barrier to resistance. Hence, as it was shown for example for the approved α-ketoamide derivatives telaprevir and boceprevir, monotherapy with NS3-4A inhibitors results in an approximately 4 $\log_{10}$ decrease of serum HCV RNA within days, but also in a rapid selection of resistant variants and viral breakthrough [10–13]. The risk of resistance development can be significantly reduced by the addition of pegIFN-α and ribavirin, and telaprevir or boceprevir-based triple therapies result in SVR rates of approximately 70–80%, 80–90%, and 30–40% in treatment-naïve HCV genotype 1 patients, previous relapsers, and null responders to pegIFN-α and ribavirin, respectively [1–4].

Another important feature of most NS3-4A protease inhibitors is the selective activity against distinct HCV genotypes, which is explained by sequence differences in important parts of the protease domain between HCV genotypes [5]. Thus far, most NS3-4A inhibitors have been developed predominantly to target HCV genotype 1. Newer NS3-4A protease inhibitors than telaprevir and boceprevir, which are currently in phase 1–3 development, include for example simeprevir (TMC435), danoprevir (R7227/ITMN191), vaniprevir (MK-7009), asunaprevir (BMS-650032), BI201335, ACH-1625, ABT-450, MK-5172, GS-9256, and GS-9451. Potential advantages of these second and third generation protease inhibitors might be improved tolerability, broader genotypic activity (e.g., MK-5172), different resistance profiles (e.g., MK-5172), and/or improved pharmacokinetics, which allow a once daily dosage (e.g., TMC435, BI201335) [14–18].

Unfortunately, the resistance profiles of linear tetrapeptide and macrocyclic inhibitors are overlapping. Amino acid position R155 in NS3 constitutes the central position for resistance development [19]. Mutations at this amino acid site confer resistance to nearly all protease inhibitors which are currently in advanced clinical development. Consequently, combining different NS3-4A inhibitors is not a logical strategy for interferon-free regimens. A possible exception is MK-5172, which exhibits potent antiviral activity against variants carrying mutations at position R155 [16].

Importantly, the genetic barrier to resistance against telaprevir (and other NS3-4A inhibitors) differs significantly between HCV genotype 1 subtypes. In all clinical studies of telaprevir alone or in combination with pegIFN-alfa and ribavirin, viral resistance and breakthrough occurred much more frequently in patients infected with HCV genotype 1a compared to HCV genotype 1b [2,4]. This difference was shown to result from nucleotide differences at position 155 in HCV subtype 1a (AGA, encodes R) *vs.* 1b (CGA, also encodes R). The mutation most frequently associated with resistance to telaprevir is R155K; changing R to K at position 155 requires 1 nucleotide change in HCV subtype 1a and 2 nucleotide changes in subtype 1b isolates [20]. Consequently, HCV genotype 1a may be a problematic subtype for successful all-oral therapy based on NS3-4A inhibitors.

An additional possible limitation of most NS3-4A inhibitors is the interaction with CYP3A4, resulting in numerous drug–drug interactions including tacrolimus, cyclosporine, antiretroviral agents, statins, antifungals, and many more [21]. This complicates their use in distinct patient populations with a high need for interferon-free regimens, such as liver transplanted patients or patients co-infected with human immunodeficiency virus (HIV).