Review paper

Viral hepatitis C treatment shortening – what is the limit?

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Abstract

Successful antiviral treatment for hepatitis C virus (HCV) infection is crucial to prevent progression of the disease and its most serious complications. Therapy options have changed over the years with improvement of treatment efficacy, safety and simplification. They evolved from interferon and ribavirin combination administered for 24-72 weeks through interferon (IFN)-based triple therapies with 24-48 weeks duration to the all-oral, well-tolerated direct-acting antiviral regimens lasting for 8-16 weeks and with almost 100% cure rates. The benefits of shorter treatment duration are cost reduction, access to therapy for more patients, and lower risk of adverse events and nonadherence. This review summarizes data on treatment options, focusing on the recommended durations of different regimens depending on HCV genotype, severity of liver disease and history of previous therapy. According to currently available data, shortening treatment below 8 weeks does not provide additional benefits, although the further simplification of therapy is still a subject of study.

Key words: interferon, direct acting antiviral, hepatitis C virus, shortening therapy.

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Introduction

Hepatitis C virus (HCV) infection is a global health issue, being a major cause of chronic liver disease worldwide. According to recent estimates of the World Health Organization (WHO), chronic hepatitis C (CHC) affects approximately 71 million individuals worldwide [1]. Based on genetic diversity HCV has been categorized into eight distinct genotypes differing in their geographical distribution, the effect on disease progression and treatment response. The most frequent is genotype (GT) 1, which accounts for more than half of all HCV infections worldwide, followed by GT3 and GT4 [2].

Antiviral treatment resulting in HCV eradication is essential in preventing progression of the disease and its most serious complications including cirrhosis, liver impairment and hepatocellular carcinoma, causing approximately 350 000 deaths annually [3].

Interferon era

In the era of interferon (IFN)-based therapy, HCV genotype was considered to be the most important predictor of treatment outcome. Patients infected with predominant GT1 and additionally GT4 were treated with pegylated interferon α (PegIFNa) and ribavirin (RBV) for 48 weeks, which was established as a standard length of interferon-based regimens with a sustained virologic response (SVR) rate of about 50%. Length of the treatment shortened to 24 weeks was possible in patients infected with GT2 and GT3, which were recognized as “easy-to-treat” because of the SVR rate up to 80% [4]. There was also the recommended option of shortening treatment to 12-16 weeks in so-called “rapid virologic responders” (undetectable HCV RNA after 4 weeks of therapy) infected with GT2 or GT3 with a low baseline viral load (< 800 000 IU/ml), but it was not applied frequently in clinical practice.
due to complicated criteria. On the other hand, in patients infected with GT1 or GT4, who demonstrated a weak on-treatment response, as well as in cirrhotics and those retreated after failure, the treatment was extended to 72 weeks in patients with later HCV RNA undetectability during therapy [5, 6].

**Interferon-based triple therapies**

The year 2011 brought the registration of telaprevir (TVR) and boceprevir (BOC), the first generation of HCV serine protease inhibitors (NS3/4A). This class of drugs comprised the first direct acting antivirals (DAA) approved for use with PegIFNa and RBV in GT1 infected patients only [7]. The triple regimens have increased the SVR rate up to 75% and allowed shortening of the treatment duration in selected patients, but still with the length of therapy up to 48 weeks in others. In non-cirrhotic relapers or treatment-naïve patients TVR-based therapy could be shortened to 24 weeks and in previously untreated patients without liver cirrhosis the BOC-based regimen could be shortened to 28 weeks [8]. Unfortunately TVR- and BOC-based triple regimens worsened the safety profile, particularly in cirrhotic patients, who additionally still demonstrated a low SVR rate [9].

Those options were quickly replaced by the other IFN-based regimens containing DAA such as sme-previr (SMV) or sofosbuvir (SOF). The combination of PegIFNa, RBV and SMV, a protease inhibitor, was registered for treatment of GT1 and GT4 infected patients for 48 weeks with possible shortening to 24 weeks in treatment-naïve patients and relapers after previous failure of PegIFNa + RBV therapy. Alongside the scope for using this regimen in GT4 infected patients, both the efficacy and safety profile were much more favorable in comparison to TVR and BOC-containing triple therapy [10]. However, the real revolution in the CHC treatment was the advent of SOF, a new DAA class representative, a HCV polymerase inhibitor (nonstructural protein 5B, NS5B), registered for patients infected with all HCV genotypes [11]. Administration of SOF in combination with PegIFNa and RBV allowed shortening of treatment to only 12 weeks, irrespective of genotype, liver fibrosis and history of previous therapy [12]. Since PegIFNa and RBV were responsible for all adverse events in this regimen and it was administered for only 12 weeks, the increase of efficacy was accompanied by improvement of tolerability. Another DAA combined with PegIFNa and RBV was daclatasvir (DCV), the first inhibitor of the HCV non-structural protein 5A (NS5A). This option was never recommended by European Association for the Study of the Liver (EASL), but in 2014 it was approved by the Polish Group of Experts for HCV to treat GT1 and GT4 infected naïve patients or relapers with or without compensated liver cirrhosis for 24 or 48 weeks depending on the viral response in the 4th and 10th weeks [8, 13]. However, due to relatively long treatment duration and unsatisfactory efficacy this regimen was not widely used.

**Genotype specific direct acting antivirals**

Sofosbuvir was the breakthrough medication for the treatment of CHC patients not only because of possible shortening of the IFN-based therapy, but also due to the fact that SOF was the first anti-HCV drug approved by the Food and Drug Administration (FDA) to use without interferon. The combination of SOF and RBV was the first IFN-free all-oral therapy for HCV infection. This regimen was recommended for use in patients infected with GT2 for 12 weeks but for GT3 treatment was still 24 weeks. The 24-week SOF + RBV regimen was also an option in patients infected with GT1, GT4, GT5 and GT6, but was recommended only in case of IFN intolerance [12].

The next step on the way to shortening the length of therapy, with increase of treatment efficacy and improvement of safety profile, was to combine two or even more DAA in one regimen. Initially, DAA with different modes of action were administered with addition of RBV in selected cases. According to initial recommendations for IFN-free therapy, patients without or with liver cirrhosis (including decompensated), infected with GT1 or GT4, could be treated with SOF and SMV for 12 weeks with or without RBV depending on presence of advanced liver fibrosis. However, for RBV intolerant patients extension to 24 weeks was recommended [12, 14]. Effectiveness of SOF + SMV combination administered according to this protocol reached over 90% [15]. Unfortunately, an attempt to apply SOF + SMV for 8 weeks resulted in a significant SVR rate reduction, so shortening of this treatment below 12 weeks was never recommended [16]. The regimen containing SOF and DCV was approved for use in patients with different stages of liver disease, including decompensated cirrhosis and infected with all HCV genotypes, with efficacy over 95% [17, 18]. Recommended treatment duration was 12 weeks for all noncirrhotic patients and cirrhotics infected with GT2 as well. However, addition of RBV or extension of therapy to 24 weeks in case of RBV intolerance was indicated in cirrhotics infected with GT1, GT4, GT5 or GT6. Cirrhotics infected with GT3 were recognized as difficult to treat and had to receive medication for 24 week with addition of RBV. De-
spite the relatively long treatment time, the SOF + DCV ± RBV regimen for patients infected with GT3 was the first highly effective alloral option with SVR significantly higher in comparison to SOF + RBV therapy [19, 20]. Unfortunately also with this regimen shortening of treatment duration to 12 or even 16 weeks has resulted in a relevant decrease of SVR [21]. The application of another dual DCV-containing regimen, consisting of DCV and the NS3/4A inhibitor asunaprevir (ASV) was intended for GT1b infected individuals only, including those with compensated liver cirrhosis. In practice, this regimen was limited to Asia and a few European countries including Poland due to the ASV registration issue [22]. The cure rate of this regimen did not exceed 90%, and there was one permitted treatment duration of 24 weeks, without any shortening option [23].

Simultaneous administration of different DAA in a single tablet simplified therapy of HCV infections. In 2014 a fixed-dose, one-pill combination of SOF and the NS5A inhibitor ledipasvir (LDV) administered once a day was approved for treatment of GT1, GT4, GT5 and GT6 infected patients. The SVR rate achieved in both clinical trials and real-world experience (RWE) studies was over 95% in different population [24]. According to the summary of product characteristics (SmPC), as well as international and national guidelines, the standard length of the LDV/SOF regimen was 12 weeks, with or without RBV depending on liver cirrhosis [11]. Additionally, for cirrhotic patients, including decompensated individuals, or those intolerant to RBV, treatment prolongation was recommended. On the other hand, for noncirrhotic treatment-naïve patients infected with GT1 shortening of therapy to 8 weeks became possible [11]. Both clinical trial (ION-3) and RWE studies have demonstrated that shortening of treatment duration did not affect efficacy in this population [25–27].

The next available all-oral regimen with effectiveness over 95% demonstrated in clinical trials, ombitasvir/paritaprevir/ritonavir (OBV/PTV/r), was approved in 2015 for the treatment of GT4, and in combination with dasabuvir (DSV) also for GT1 infected patients. The regimen was not comparable to SOV/LDV, because of the two-pill combination administered twice a day, but in RWE studies it demonstrated an SVR rate up to 99% even in patients with advanced liver disease [28]. At the very beginning, patients infected with GT1b were treated with OBV/PTV/r + DSV for 12 weeks, with addition of RBV if cirrhosis was diagnosed. Patients infected with GT1a required OBV/PTV/r + DSV and RBV therapy for 12 weeks in non-cirrhotics and 24 weeks in cirrhotics. Non-cirrhotics infected with GT4 received OBV/PTV/r + RBV without DSV for 12 weeks, whereas cirrhotics received it for 24 weeks [29]. Several updates of SmPC, based on the results of clinical trials, simplified treatment with OBV/PTV/r ± DSV ± RBV. The first crucial change was implemented after the Turquoise-III study and since April 2016 patients with GT1b and compensated liver cirrhosis have been treated for 12 weeks without RBV with the same efficacy, but improved safety [30]. The second update based on the Agate-1 trial results shortened therapy of patients infected with GT4 to 12 weeks [31]. Finally, after the Garnet study treatment-naïve patients with minimal to moderate fibrosis, infected with GT1b, became eligible to receive the OBV/PTV/r + DSV regimen for 8 weeks only. The high efficacy of the shortened treatment course in this subpopulation was confirmed by real-world studies, but according to the Epiter-2 decision on shortening one should be careful in males because of the SVR reduction risk [32–34].

The third genotype-specific DAA single-pill regimen approved for treatment of patients without or with compensated liver cirrhosis has been available since July 2016. The fixed-dose, one-pill combination of grazoprevir (GZR), NS3/4A inhibitor, and elbasvir (EBR), which blocks the NS5A complex, was intended for GT1 and GT4 infected patients with standard therapy duration of 12 weeks, which assured an SVR rate over 95% [35]. According to SmPC and guidelines prolongation of treatment to 16 weeks was recommended in the case of presence of a specific NS5A polymorphism and baseline viral load over 800 000 IU/ml in patients infected with GT1a and GT4 [36]. On the other hand, high efficacy (97%) of the shortened GZR/EBR regimen in GT1b infected patients with non-advanced liver fibrosis demonstrated recently in the phase-3 Streager study supports possible 8-week therapy in such a population [37].

**Pangenotypic regimens**

Genotype-specific therapeutic options did not cover all HCV infected populations, so availability of potent pangenotypic regimens since again changed the landscape of HCV treatment. The fixed-dose combination of SOF and velpatasvir (VEL), targeting the viral protein NS5A, was the first one-pill pangenotypic regimen that could be administered in patients infected with any HCV genotype for 12 weeks irrespective of liver fibrosis, including decompensated cirrhosis, with an overall cure rate of 95% or over [38]. Although recommended treatment duration was 12 weeks, the RWE study conducted by Boyle et al. in previously untreated noncirrhotic infected with GT3 on opioid substitution therapy documented an SVR rate of 100% with 8-week
treatment duration [39]. Addition of the NS3/4A inhibitor voxilaprevir (VOX) to SOF/VEL made this single-tablet, triple regimen successful in 91-100% of patients, depending on HCV genotype, liver fibrosis and history of previous therapy [40]. Based on the results of clinical trials, treatment duration of 12 weeks is currently recommended for all DAA treatment-experienced patients regardless of liver fibrosis and DAA treatment-naïve cirrhotics. Non-cirrhotics, naïve to DAA treatment, could receive therapy shortened to 8 weeks. This short regimen can also be considered in GT3 infected cirrhotics [41].

The regimen providing an opportunity for shortening treatment to 8 weeks in the majority of patients is a combination of the NS3/4A inhibitor glecaprevir (GLE) and the NS5A inhibitor pibrentasvir (PIB), which was demonstrated to cure 98% of patients. According to current recommendations, patients eligible for 8-week therapy are all non-cirrhotic patients except those infected with GT3 previously exposed to SOF-containing regimens [42-44]. For other subpopulations longer treatment duration is recommended, 12 weeks for treatment-naïve cirrhotic patients infected with all genotype and SOF-experienced GT1, GT2, GT4-6, and even 16 weeks for GT3 patients previously treated with PegIFNa + RBV ± SOF or SOF + RBV. However, recently presented results of the EXPEDITION-8 study demonstrated that also compensated cirrhosis can be treated for 8 weeks without risk of efficacy reduction [45]. This conclusion has already changed SmPC, so since July 2019 previously untreated patients with compensated liver cirrhosis infected with GT1, GT2, GT4-6 have been treated for 8 weeks [46].

Can we go below 8 weeks?

The possibility of further shortening HCV treatment duration has been investigated in numerous clinical trials [47-51]. In the phase 2 study FOURward the efficacy of a four-DAA combination – DCV, ASV, SOF and the NS5B inhibitor beclabuvir (BCV) – administered for 6 weeks was examined. The cure rate in a cohort of treatment-naïve GT1 infected patients reached 57%, which is suboptimal [47]. A higher cure rate of 87%, but still not good enough, was obtained after 6-week administration of SOF/GZR/EBR in treatment-naïve non-cirrhotic patients in the C-SWIFT study [48]. Much more promising results with an SVR of 95% were obtained in 6-week treatment of SOF/LDV combined with the NS5B inhibitor radalbuvir or the NS3/4A inhibitor GS-9451 in a phase 2 clinical trial [49]. The same cure rate was demonstrated in the phase 3 study OMEGA-1 for 6-week treatment with the JNJ-4178 regimen consisting of three direct acting antivirals – SMV, the NS5A inhibitor odalasvir, and the NS5B inhibitor AL-335 – administered in noncirrhotic GT1,

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**Fig. 1.** Length of particular regimens administered for treatment of HCV infections
GT2, GT4 and GT5 infected patients [50]. The high efficacy with SVR of 93% was also confirmed for the 6-week regimen of SOF/VEL and the novel NS3/4A inhibitor GS-9857 in treatment-naïve noncirrhotic patients [51]. Despite promising results, these data must be confirmed in larger groups of patients.

Studies assessing all-oral 4-week antiviral regimens in GT1 infected patients have not provided such optimistic results so far. Combination of SOF/LDV/VOX, SOF/DCV/ASV/BCV and SOF/GZR/EBR resulted in SVR of 27%, 29% and 39%, respectively [41, 47, 48]. The SVR rate after 4-week treatment with SOF/LDV + GS-9451 or SOF/LDV + GS-9451 + GS-9799 (NS5B inhibitor) was 40% and 20% respectively [52]. A promising way to shorten treatment length under 8 weeks without affecting the efficacy could be response-guided therapy, which is the subject of several early-phase clinical trials [53, 54].

Conclusions

The introduction of IFN-free regimens revolutionized the HCV treatment landscape, making therapy much more effective and tolerable. The treatment simplification also includes shortening of the therapy course (Fig. 1). Currently we have a possibility to apply 8-week regimens in the majority of HCV infected patients with excellent efficacy, but studies assessing opportunities to further reduce treatment length are still ongoing. Eight-week regimens are currently approved in easy-to-treat patient populations with SOF/LDV, OBV/PTV/r + DSV, GLE/PIB and VOX/SOF/VEL. Available data demonstrated such a possibility also for GZR/EBR and SOF/VEL regimens, but they are not registered and are not recommended yet. According to currently available data, shortening of treatment duration to 4 weeks is unlikely. Application of 6-week regimens is possible in some populations selected with response-guided therapy. However, the cost of such selection could be higher than the expected savings.

Disclosure

The author reports no conflict of interest.

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