Marmara Medical Journal 2016; 29 (Special issue 1): 43-49
DOI: 10.5472/MMJsi.2901.09

REVIEW / DERLEME

New treatments for chronic hepatitis C infection

Kronik hepatit C tedavisinde yeni gelişmeler

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ABSTRACT

The goal of HCV treatment is to prevent cirrhosis, hepatocellular carcinoma, liver-related deaths. The development of direct-acting antiviral (DAA) agents which target various steps in HCV lifecycle led to a revolution by providing nearly complete eradication of HCV. The new treatment regimens with high cure rates have changed the standards of care in the regions where patients have access to new treatments. This review addresses the recent updates in management of chronic hepatitis C infection.

Keywords: Hepatitis C, New treatments, Direct antiviral agents

ÖZ

Hepatit C tedavisinde amaç siroz, siroza bağlı komplikasyonları ve hepatosellüler karsinoma gelişmesi risklerini azaltmak veya tamamiyle ortadan kaldırmaktır. HCV tedavisinde son yıllarda çok önemli gelişmeler kaydedilmiştir. Yeni geliştirilen ve HCV virusunun çoğalmasını engelleyen direkt etkili antiviral ilaçlar ile tama yakın oranlarda virusun eradikasyonu sağlanmaktadır. Bu derlemede yeni geliştirilen bu ilaçlar ile tedaviler detaylı olarak ele alınacaktır.

Anahtar kelimeler: Hepatit C, Yeni tedaviler, Direkt antiviral ajanlar

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Introduction

Chronic hepatitis C infection is a global public health problem which is responsible for the majority of liver-related deaths, mostly because of HCV-associated cirrhosis and hepatocellular carcinoma. With the advent of highly effective HCV protease inhibitor (PI) therapies in 2011, treatment of chronic hepatitis C showed a rapid shift from 'modest treatment response' to 'complete cure'.

The combination of pegylated interferon (Peg-IFN)- and ribavirin for 24 or 48 weeks of treatment was the standard of care in hepatitis C with sustained virologic response (SVR) rate of 40-50% in HCV genotype 1 infection [1-3]. The approval of first generation direct-acting antivirals (DAAs) increased the response rates up to 65% - 75% [4-7]. However, the side effects of the triple combination therapy, and the lower efficacy in patients with advanced hepatic fibrosis were the major limitations of these treatments. Ultimately, IFN-free regimens with >90% SVR rates, good safety profile and shorter treatment duration have changed the fate of chronic hepatitis C by providing almost a cure in patients with advanced fibrosis and cirrhosis. This article reviews the new treatment strategies of hepatitis C infection based on the recommendations of American (AASLD) and European (EASL) Liver Societies.

When to initiate therapy and for which patients ?

Treatment is recommended in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. As the success of treatment indicates the virologic cure, treatment is also being advocated as a means to prevent HCV transmission. Considering the high cost of the new antivirals, priorities may be adapted according to the societal and economic conditions. Urgent initiation of

treatment is recommended for patients with advanced fibrosis or compensated cirrhosis and decompensated cirrhosis. In patients with HIV or HBV co-infection and patients with extra-hepatic manifestations (i.e. Symptomatic vasculitis associated with HCV-related mixed cryoglobulinemia, HCV immune complex-mediated nephropathy, non-Hodgkin B cell lymphoma), and patients with debilitating fatigue, patients at risk of transmitting HCV; treatment should be prioritized regardless of the fibrosis stage. Treatment is justified in patients with moderate fibrosis (METAVIR score F2). Treatment and timing of therapy can be individualized in patients with no or mild disease (METAVIR score F0-F1) [8,9].

An overview of treatment regimens

Peg-IFN therapy with Ribavirin

In early 2000s, combination therapy with Peg-IFN and Ribavirin initiated a new era in the treatment of chronic HCV. However, Peg-IFN and Ribavirin therapy resulted in SVR in 45% of genotype 1 patients [1-3] and low tolerability of IFN-based treatments further decreased the hope for cure in this group of patients. Higher SVR rates were achieved in patients with HCV genotypes 2,3 and 5, and intermediate SVR rates were achieved in HCV genotype 4 infection [10].

Protease inhibitors

A new class of direct-acting antiviral agents (DAAs) target specific enzymes involved in viral replication. The addition of these new protease inhibitors (PIs) to pegylated interferon and ribavirin further improved the treatment responses.

The second generation HCV NS3/4A protease inhibitors Boceprevir and Telaprevir were approved by the US Food and Drug Administration (FDA) in May 2011 [4-7]. However, treatment with either of these agents is no longer recommended because of their poor tolerability, considerable side effects and current availability of highly efficient regimens that contain sofosbuvir or simeprevir [8,9].

Simeprevir, a second generation PI was approved in November 2013 [11]. Simeprevir has increased efficacy for Genotype 1 HCV, orally administered as a 150 mg capsule daily with food. Simeprevir should not be used in patients who have treatment failures with first generation PIs because of the risk of overlapping resistance. Simeprevir use in combination with Peg-IFN and Ribavirin is indicated for HCV genotype 1 infection in patients with compensated liver disease including cirrhosis who are treatment-naive and treatment-experienced. In November 2014, simeprevir plus sofosbuvir treatment has been approved for treatment-naive and treatment-experienced patients with 12 week duration for patients without cirrhosis and 24 week for patients with cirrhosis. The presence of baseline Q80K genetic polymorphism, which is commonly found in genotype 1a patients, decreased the efficacy of simeprevir substantially and therefore its use is not recommended in this group.

Polymerase inhibitors

HCV NS5B polymerase plays an essential role in HCV replication. Sofosbuvir is an NS5B polymerase inhibitor that results in suppression of HCV replication and life cycle. Sofosbuvir is a nucleotide analogue that potentially inhibits HCV replication through interference with RNA-dependent RNA polymerase function. Sofosbuvir was approved in December 2013 by FDA, and by the European Medical Agency (EMA) in 2014. Sofosbuvir has pangenotypic efficacy and cannot be used as monotherapy. Combination treatment with ribavirin or Peg-IFN plus ribavirin was investigated in the phase trials [12,13]. In all phase 3 studies, no viral resistance to sofosbuvir was detected among patients who relapsed after completion of treatment. Daily dose of 400 mg per os is generally well tolerated. Sofosbuvir use is not approved in patients with creatinine clearance <30 mL/min.

A combination oral regimen containing ledipasvir (NS5A protease inhibitor) and sofosbuvir was approved by FDA in October 2014 for HCV genotype 1 infection. The dose is once daily and administered without Peg-IFN or ribavirin. SVR rate is 94-99% in treatment-naive, treatment-experienced patients, and in patients with cirrhosis and without cirrhosis [14-16].

Daclatasvir, is the first NS5A inhibitor suppressing HCV RNA synthesis, first approved in Japan and recently approved by FDA in July 2015 [17]. The efficacy is pangenotypic. The dose is 60 mg once daily concomitant with sofosbuvir.

Combination regimens

The combination of paritaprevir/ombitasvir/ritonavir and dasubuvir was approved by FDA in December 2014 for genotype 1 and in July 2015 for genotype 4 HCV infection.

Selection of treatment regimens

Selection of treatment regimens should be based on the viral genotype, prior treatment experience, presence of cirrhosis, comorbidities (especially renal insufficiency), concurrent medications that interact with DAAs. DAAs should not be used as monotherapy because of the risk of drug resistance and treatment failure.

Genotype 1

Recently updated AASLD-IDSA guideline no longer recommends Peg-IFN and dibavirin combination regiments with sofosbuvir or simeprevir in genotype 1 and 2 while EASL still keeps its recommendation [8,9]. Treatment recommendations of AASLD-IDSA and EASL for HCV genotype 1 infection are summarized in Table I.

Table I. Treatment recommendations of AASLD-IDSA and EASL for HCV genotype 1

	Treatment Recommendations
Treatment-naive	
No cirrhosis	**AASLD-IDSA and EASL** Daclatasvir + Sofosbuvir (12 wk) Ledipasvir/Sofosbuvir (12 wk)[a] Paritaprevir/ritonavir/ombitasvir/dasabuvir ± Ribavirin (12 wk)[b] Simeprevir + Sofosbuvir (12 wk) **EASL** Peg-IFN + Ribavirin + Sofosbuvir (12 wk) [Peg-IFN + Ribavirin] (24 wk) + Simeprevir (12 wk)[c]
Cirrhosis	**AASLD-IDSA and EASL** Daclatasvir + Sofosbuvir ± Ribavirin (12-24 wk)[e] Ledipasvir/Sofosbuvir (12 wk) Paritaprevir/ritonavir/ombitasvir/dasabuvir ± Ribavirin (12 wk)[b] Simeprevir + Sofosbuvir ± Ribavirin (12-24 wk) [e]
Treatment-experienced	
No cirrhosis	**AASLD-IDSA and EASL** Daclatasvir + Sofosbuvir ± Ribavirin (12 - 24 wk)[f] (12 wk) Ledipasvir/Sofosbuvir ± Ribavirin (12 - 24 wk)[f] Paritaprevir/ritonavir/ombitasvir/dasabuvir ± Ribavirin (12 wk)[b] Simeprevir + Sofosbuvir (12 wk) **EASL** Peg-IFN + Ribavirin + Sofosbuvir (12 wk) [Peg-IFN + Ribavirin] (24 wk) + Simeprevir (12 wk)[c]
Cirrhosis	**AASLD-IDSA and EASL** Daclatasvir + Sofosbuvir ± Ribavirin (24 wk) Ledipasvir/Sofosbuvir (12 wk)[f,g] Paritaprevir/ritonavir/ombitasvir/dasabuvir ± Ribavirin Simeprevir + Sofosbuvir ± Ribavirin (24 wk) **EASL** Peg-IFN + Ribavirin + Sofosbuvir (12 wk) [Peg-IFN + Ribavirin] (24 wk) + Simeprevir (12 wk)[c]

[a] Treatment duration may be shortened to 8 weeks if baseline HCV RNA is <6 million IU/mL, [b] Genotype 1a patients should receive paritaprevir/ritonavir/ombitasvir/dasabuvir combination with Ribavirin. Genotype 1b patients are not recommended to receive Ribavirin with paritaprevir/ritonavir/ombitasvir/dasabuvir combination. EASL recommends addition of Ribavirin only in genotype 1b patients who have cirrhosis, [c] This combination is not recommended in patients with Q80K mutations. Peg-IFN and Ribavirin is administered for 24 weeks; including 12 week combination treatment with Simeprevir, [d] Patients with compensated cirrhosis who have contraindications to Ribavirin should receive 24 weeks of treatment, [e] Patients with cirrhosis who have contraindications to Ribavirin treatment should receive 24 week treatment, [f] EASL recommends 12 week treatment with Ribavirin, 24 week without Ribavirin while AASLD does not recommend Ribavirin combination, [g] Patients with cirrhosis in whom HCV protease inhibitor plus Peg-IFN and Ribavirin treatment have failed should receive ledipasvir/sofosbuvir for 24 weeks.

Table II. Treatment recommendation for HCV Genotype 2-6 infection

	Treatment Recommendations
Genotype 2	
Treatment-naive	
No cirrhosis	Sofosbuvir + Ribavirin (12 wk) Daclatasvir + Sofosbuvir (12 wk) Peg-IFN + Ribavirin + Sofosbuvir (12 wk)[a]
Cirrhosis	Sofosbuvir + Ribavirin (16 wk) Peg-IFN + Ribavirin + Sofosbuvir (12 wk)[a] Daclatasvir + Sofosbuvir ± Ribavirin (12 wk)[b]
Treatment experienced	
No cirrhosis	Sofosbuvir + Ribavirin (16 or 24 wk) Peg-IFN + Ribavirin + Sofosbuvir (12 wk) Daclatasvir + Sofosbuvir ± Ribavirin (12 wk)[b]
Cirrhosis	Sofosbuvir + Ribavirin (16 or 24 wk) Peg-IFN + Ribavirin + Sofosbuvir (12 wk) Daclatasvir + Sofosbuvir ± Ribavirin (12 wk)[b]
Genotype 3	
Treatment-naive	
No cirrhosis	Daclatasvir + Sofosbuvir (12 wk) [c] Peg-IFN + Ribavirin + Sofosbuvir (12 wk) Sofosbuvir + Ribavirin (12-24 wk)
Cirrhosis	Daclatasvir + Sofosbuvir ± Ribavirin (24 wk)[d] Peg-IFN + Ribavirin + Sofosbuvir (12 wk)
Treatment experienced	
No cirrhosis	Daclatasvir + Sofosbuvir (12 wk) Sofosbuvir + Ribavirin[e] Peg-IFN + Ribavirin + Sofosbuvir (12 wk)
Cirrhosis	Daclatasvir + Sofosbuvir ± Ribavirin (24 wk)[d] Peg-IFN + Ribavirin + Sofosbuvir (12 wk)[e]
Genotype 4	
	Peg-IFN + Ribavirin + Sofosbuvir (12 wk) Ledipasvir/Sofosbuvir (12-24 wk)[f] Paritaprevir/ritonavir/ombitasvir + Ribavirin (12 -24wk)[f] Sofosbuvir + Ribavirin (24 wk) Peg-IFN+ Ribavirin + Simeprevir (12 -36 wk)[f,g] Sofosbuvir + Simeprevir (12 -24 wk)[f,g] Sofosbuvir + Daclatasvir (12 -24 wk)[f,g]
Genotype 5 or 6	
	Peg-IFN + Ribavirin + Sofosbuvir (12 wk) Ledipasvir/Sofosbuvir (12 wk) Sofosbuvir + Daclatasvir (12-24 wk)[f,g]

[a] AASLD recommends Peg-IFN + Ribavirin + Sofosbuvir treatment as an alternative regimen for HCV genotype 2 infection for patients who are eligible to Peg-IFN and in whom previous Peg-IFN and Ribavirin treatment failed, [b] AASLD recommends Daclatasvir and Sofosbuvir with or without Ribavirin for 24 weeks in HCV genotype 2 patients who are ineligible to receive IFN and in whom previous sofosbuvir and Ribavirin has failed, [c] AASLD recommends Sofosbuvir and Ribavirin for 12 weeks in IFN-eligible HCV genotype 3 infection and for 24 weeks in IFN-eligible genotype 3 infection cirrhosis and in whom previous Peg-IFN and Ribavirin failed., [d]AASLD recommends Daclatasvir and Sofosbuvir with Ribavirin for 24 weeks in HCV genotype 3 patients with cirrhosis and in whom previous Peg-IFN and Ribavirin failed, [e] EASL recommends 24-week Sofosbuvir and Ribavirin for treatment-naïve HCV genotype 3 infection and does not recommend for patients who have cirrhosis and in whom previous Peg-IFN and Ribavirin treatment failed. Alternatively, AASLD recommends addition of Peg-IFN to sofosbuvir and Ribavirin treatment in previous IFN non-responder patients and in IFN eligible patients, [f] 24-week treatment is recommended in patients with cirrhosis, [g] Recommendations of EASL.

Since the relapse rates are higher in HCV genotype 1a, management of genotype 1-infected patients should be based on HCV subtype. IFN-free regimens such as ledipasvir-sofosbuvir, daclatasvir-sofosbuvir (with or without RBV), paritaprevir/ ombitasvir/ritonavir plus dasabuvir (with or without RBV), and simeprevir-sofosbuvir (with or without RBV) have high efficacy and safety.

Registration trials of ledipasvir-sofosbuvir (ION-1) found that SVR rate at 12 weeks (SVR12) in treatment naive HCV genotype-1 patients was 97% to 99% regardless of treatment duration (12 or 24 week treatment), presence of cirrhosis, RBV use and genotype 1 subtype [14].

A further analysis of these patients (ION-3 trial) excluding the cirrhotics investigated how shortening the treatment from 12 weeks to 8 weeks would affect the outcome [16]. SVR12 rate was 93-95%, relapse rates were higher in patients who received 8 week treatment, particularly in those who had baseline HCV RNA above 6 million IU/mL. For treatment-naive patients with a viral load of >6 million IU/mL or with cirrhosis, ledipasvir/sofosbuvir is recommended for 12 weeks. Treatment-experienced patients who have had PEG-IFN and RBV failure, ledipasvir/sofosbuvir is recommended for 12 weeks and 24 weeks in non-cirrhotics and cirrhotics, respectively. In cirrhotic patients, addition of RBV can decrease the treatment duration from 24 weeks to 12 weeks.

Daclatasvir-sofosbuvir for 12 weeks (in non cirrhotics) or 24 weeks (in cirrhotic patients) in combination with or without weight-based RBV (cirrhosis) is recommended for treatment-naive patients and for patients in whom prior Peg-IFN and ribavirin treatment has failed. The recommendation is based on the ALLY-2 trial which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in HIV and HCV co-infected patients [18]. SVR rate was 96% in treatment naive patients and 82% in treatment-experienced patients. As the number of cirrhotic patients is small in the registration trials, addition of ribavirin and extending the treatment duration to 24 weeks is recommended in difficult-to treat patients.

Combination therapy of paritaprevir/ ombitasvir/ritonavir and dasubuvir was approved by the FDA for the treatment of HCV genotype 1 based on SAPPHIRE-1, PEARL-III, PEARL-IV and TURQUOISE-I trials [19-23]. The SAPPHIRE-I trial reported SVR12 rate of 95.3% and 98% with 12 weeks of PrOD and RBV in HCV genotype 1a and 1b, respectively [19]. PEARL III trial showed that SVR12 was lower in the RBV-free arm than in the RBV-containing arm (90% vs 97%, respectively). In contrast PEARL-IV trial showed that there is no added benefit from the use of weight-based RBV for patients without cirrhosis who have HCV genotype 1b infection [22]. In treatment-naive and treatment experienced HCV genotype 1a patients, 12 week treatment regimen with RBV in noncirrhotics and 24 week in cirrhotics were recommended, respectively. In genoype 1b HCV infection, 12 week of PrOD treatment without ribavirin in non-cirrhotics and 12 week of treatment with ribavirin in cirrhotics are recommended both in treatment-naive and treatment-experienced patients.

The OPTIMIST-1 trial which examined the safety and efficacy of simeprevir plus sofosbuvir in treatment-naive and treatment-experienced patients without cirrhosis [24] showed SVR12 rate of 97% with 12-week treatment and 83% with 8-week treatment. OPTIMIST-2 trial investigated the efficacy of simeprevir plus sofosbuvir treatment in treatment-naive and treatment-experienced cirrhotic patients [25]. The SVR12 rate was 88% in treatment-naive and 79% in treatment-experienced patients. As the response rate is lower in cirrhotic patients with genotype 1a infection and Q80K mutation, the use of this combination is not recommended.

Genotype 2

Peg-IFN and Ribavirin treatment for 24 weeks is highly effective in genotype 2 HCV infection with SVR rate of 74% (64-93%) [26]. Sofosbuvir plus weight-based ribavirin treatment resulted in 94% SVR rate in genotype 2 HCV patients [12]. Daily sofosbuvir plus weight-based Ribavirin for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection, and extending treatment duration to 16 weeks is recommended for treatment experienced patients and cirrhotic patients. For patients who cannot tolerate ribavirin, daclatasvir and sofosbuvir can be an alternative option.

Since most patients are ineligible, intolerant or unwillling for IFN-based regimens sofosbuvir plus weight-based ribavirin treatment is recommended by the professional societies. However, in patients who do not have access to newer DAAs and who can tolerate IFN-based regimens, Peg-IFN and ribavirin treatment can still be considered. Treatment recommendations of AASLD-IDSA and EASL for genotype 2-6 were summarized in Table II.

Genotype 3

Compared to Genotype 2, Genotype 3 HCV infection is less responsive to Peg-IFN and Ribavirin treatment. SVR rate for 24 week Peg-IFN and Ribavirin treatment is 60-80%

[26]. When the Peg-IFN and Ribavirin was the first-line treatment, genotype 1 was the least responsive genotype. With the introduction of DAAs, genotype 3 has become the most difficult-to-treat genotype.

The preferred DAA regimen is based on the ALLY-3 trial which reported 97% SVR12 rate in treatment-naive patients with cirrhosis and 58% SVR12 rate in treatment-naive patients without cirrhosis [27]. Data from European cohort studies showed that extending the treatment duration to 24 weeks in cirrhotic patients increased SVR12 rate to 88% [28]. Therefore, daclatasvir plus sofosbuvir for 12 weeks in non-cirrhotics or for 24 weeks in cirrhotics (with addition of ribavirin) is recommended.

Data regarding the alternative options is limited for genotype 3 HCV infection. Sofosbuvir and weight-based ribavirin for 24 weeks can be considered in treatment-naive patients with HCV genotype 3 infection.

Genotype 4

Egypt has the highest HCV prevalance in the world at 14.7%, comprising 90% of genotype 4 HCV patients [29]. Peg-IFN and ribavirin treatment for 48 weeks had approximately 30% SVR rate and no longer recommended for genotype 4 infection. The data for selection of treatment is generally based on small studies. The recommended DAA regimens are ledipasvir/sofosbuvir for 12 weeks; paritaprevir/ritonavir/ombitasvir and weight-based ribavirin for 12 weeks; or sofosbuvir and weight-based ribavirin for 24 weeks. Sofosbuvir and weight-based ribavirin plus weekly PEG-IFN for 12 weeks is an acceptable regimen as well.

Genotype 5 and 6

The data is very limited to guide decision making for patients with genotype 5 and 6. The recommended regimen is ledipasvir/sofosbuvir for 12 weeks.

Conclusion

Chronic HCV infection is a major public health problem because of the risk of liver cirrhosis and HCV-assiciated hepatocellular carcinoma. The development of DAAs provided cure of HCV with a good tolerability profile and shorter duration of treatment. The major challenges of treatment with the IFN-free regimens are the high cost and the non- availability in the developing countries. In Turkey, IFN-free regimens are available but few patients can get access to treatment as the reimbursement is not approved by The Ministry of Health at the present time. In the future, global access to IFN-free regimens will also play a front-line role in tackling HCV epidemics by reducing the transmission of HCV infection.

Key points

- Direct-acting antiviral (DAA) agents target various steps in HCV lifecycle and provide eradication of HCV with highly effective interferon (IFN)-free regimens.
- IFN-free regimens have >90% SVR rates, good safety profile and offer shorter treatment duration and cure in patients with advanced fibrosis and cirrhosis.
- As the success of treatment indicates the virologic cure, treatment is recommended in all HCV-infected persons, except those with limited life expectancy. When resources are constrained, treatment should be prioritized for patients who benefit most from antiviral treatment.

Disclosures: Suna Yapali and Nurdan Tozun have nothing to disclose.

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