EFFICACY OF INTERFERON-FREE TREATMENT FOR PATIENTS WITH CHRONIC HEPATITIS C VIRUS

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Summary. The new direct-acting antiviral agents (DAA) have revolutionised the treatment of patients with chronic hepatitis C virus (HCV) infection. With the development of new potent DAA and the approval of different DAA combinations, cure rates of HCV infection of >90% are achievable for almost all HCV genotypes and stages of liver disease. Currently available DAA target different steps in the HCV replication cycle, in particular the NS3/4A protease, the NS5B polymerase, and the NS5A replication complex. Treatment duration varies between 8 and 24 weeks depending on the stage of fibrosis, prior treatment, HCV viral load, and HCV genotype. Ribavirin is required only for some treatment regimens and may be particularly beneficial in patients with cirrhosis. Conclusion: With the new, almost side effect-free DAA treatment options chronic HCV infection became a curable disease.

Key-words: viral hepatitis C, direct-acting antiviral agents, DAA, treatment.

Rezumat. Eficacitatea tratamentului cu interferon-free în hepatita cronică virală C

Noii agenți antivirali cu acțiune directă (DAA) au revoluționat tratamentul pacienților cu infecție cronică cu virusul hepatitei C (VHC). Odată cu dezvoltarea DAA potențială nouă și aprobarea diferitelor combinații DAA, ratele de vindecare ale infecției cu HCV de >90% sunt realizabile pentru aproape toate genotipurile VHC și stadiile bolii hepatice. DAA disponibilă în prezent vizează diferite etape ale ciclului de replicare a HCV, în special proteaza NS3/4A, polimeraza NS5B și complexul de replicare NS5A. Durata tratamentului variază între 8 și 24 de săptămâni, în funcție de stadiul fibrozei, tratamentul anterior, încărcătura virală VHC și genotipul VHC. Ribavirina este necesară numai pentru unele regimuri de tratament și poate fi deosebit de benefică la pacienții cu ciroză. Concluzie: Cu noua opțiune de tratament DAA, aproape fără efecte secundare, infecția cronică cu HCV a devenit o boală curabilă.

Cuvinte-cheie: hepatită virală C, agenți antivirali cu acțiune directă, DAA, tratament.

Резюме. Эффективность лечения пациентов с хроническим вирусным гепатитом С без интерферона

Новые противовирусные препараты прямого действия (DAA) произвели революцию в лечении пациентов с хронической инфекцией вирусом гепатита С (HCV). С разработкой нового мощного DAA и одобрением различных комбинаций DAA, уровни излечения инфекции HCV >90% достижимы для почти всех генотипов HCV и стадий заболевания печени. Доступные в настоящее время DAA нацелены на различные стадии цикла репликации HCV, в частности протеазу NS3 / 4A, полимеразу NS5B и комплекс репликации NS5A. Продолжительность лечения варьируется от 8 до 24 недель в зависимости от стадии фиброза, предшествующего лечения, вирусной нагрузки ВГС и генотипа ВГС. Рибавирин необходим только для некоторых схем лечения и может быть особенно полезным у пациентов с циррозом печени. Заключение: с новыми, почти без побочных эффектов вариантами лечения DAA хроническая инфекция HCV стала излечимой болезнью.

Ключевые слова: вирусный гепатит С, противовирусные препараты прямого действия , DAA, лечение

Introduction

Hepatitis C virus (HCV) infection remains a challenging health problem in the world. It is estimated that approximately 71.1 million people, which account for 1.0% of the world's population, are HCV carriers. Among patients with chronic HCV infection, about 20% of them will evolve to cirrhosis over a period of 20–30 years. Once cirrhosis is established, the annual rates of developing hepatic decompensation and hepatocellular carcinoma (HCC) are 3–6% and 1–4%, respectively. In addition to increasing the risks of liver-related morbidity and mortality, HCV infection is also associated with various extra-hepatic manifestations which further compromised the patients' health outcome and quality of life (2). On the other hand, the morbidity and mortality are significantly reduced once these patients achieve sustained virologic response (SVR) by anti-HCV agents. The use of interferon (IFN)-free direct acting antiviral agents (DAAs) has made a paradigm shift and become the standard of care for HCV infection. An association between sustained virological response (SVR) and a prolonged

overall survival in hepatitis C patients with advanced liver fibrosis has recently been established (5). Until 2011, the existing standard therapy consisting of the administration of pegylated interferon α (peg-IFN) in combination with ribavirin (RBV) reached SVR rates from 30 to 90% depending on HCV genotype (GT) and stage of liver disease(8). Despite SVR rates of up to 90%, patients had to face sometimes severe side effects (flu-like symptoms, leukopenia, thrombocytopenia, depression, etc.), and ribavirin poses a high risk of anemia. Furthermore, patients with mental illness, cirrhosis, or other comorbidities are ineligible for interferon-containing therapies. In stark contrast to the system-wide innate immune activation induced by interferon, the next major advance in HCV therapy employed a far more directed strategy. Direct acting antiviral agents (DAAs) have been designed to interfere with HCV replication by directly targeting HCV proteins. In 2014, Japan became the first country to approve an interferon-free therapy for HCV and has since successfully treated tens of thousands of patients. Not all patients achieve SVR, however, and pre-existing or treatment-emergent resistance associated variants contribute to treatment failure in an important subset of patients. Therefore, clinicians attempting to apply DAA therapy treatment must understand the effects of each drug and be cognizant of their resistance characteristics (1). In 2014/2015, seven new DAA obtained the approval of the European Medicines Agency (EMA), and IFN-free treatments became available for the first time. There may be economic considerations that peg-IFN-based therapies are still reasonable in some situations. For example, dual peg-IFN/RBV may still be the preferred treatment option for GT3 patients with low baseline viral load and mild fibrosis where SVR (6). Increased access to highly effective direct-acting antivirals (DAAs) for the treatment of infection with the hepatitis C virus (HCV) is revolutionizing the prospect of ending HCV epidemics. Globally, the number of people who initiated DAA-based treatment for HCV rose between 2015 and 2016, from approximately 1 million to 1.5 million (7). Requirements for the clinical development of DAA included an understanding of each step of the HCV replication cycle. Through the breakdown of the structure of HCV replicons detailed molecular studies allowed an in vitro screening of small molecules with activity against HCV(6).

Protease Inhibitors (-previrs). For the cleavage of HCV polyproteins the multifunctional protein NS3 with a serine protease activity is essential. Simeprevir In May 2014, the EMA (European Medicines Agency) approved the first once-daily, secondgeneration NS3/4A protease inhibitor simeprevir. The approval includes HCV infections with GT1 and GT4, but small pilot studies also showed an efficacy against GT2 and GT6 but not GT3. A phase III study for approval was performed in combination with peg-IFN-α-2a or -2b and RBV and showed an increased SVR up to 80–81% versus 50% for the traditional treatment with peg-IFN and RBV alone (6).

NS5A Inhibitors (-asvirs). The non-structural protein NS5A plays an important role in the building of replication complexes, viral packaging, and mounting of the HCV. In contrast to the protease inhibitors, NS5A inhibitors have therefore shown the strongest antiviral efficacy until now. Thus, NS5A inhibitors are components of almost all approved IFN-free DAA regimes or evaluated in phase III studies (6). Daclatasvir first approved by the US Food and Drug Administration on 24 July 2015. Daclatasvir is part of the preferred regimen for infection with genotypes 1, 3 and 4 in the WHO 2016 Guidelines for the screening, care and treatment of persons with chronic HCV infection (6). The combination of DCV with ASV showed cure rates of 82–90% for GT1b in a phase III study and is available for the therapy of HCV GT1 infection in Japan. The combination of low-dose DCV (30 mg instead of 60 mg once daily) with SMV showed less SVR12 rates of overall 75–85% in treatment naïve GT1-infected patients. Since November 2014, ledipasvir (LDV) in combination with SOF is available as fixed-dose combination (HARVONI; 90/400 mg once daily) for the therapy of GT1, GT3, and GT4 (6).

NS5B Inhibitors (-buvirs). Non-Nucleoside Polymerase Inhibitors Non-nucleoside polymerase inhibitors (‘Non-NUCs’) are currently only part of NUC-free combination therapies against HCV GT1 infection. Sofosbuvir was first approved by the US Food and Drug Administration on 6 December 2013, and by the European Medicines Agency in January 2014. Sofosbuvir is part of the preferred regimen for all six major genotypes in the WHO 2016 Guidelines for the screening, care and treatment of persons with chronic HCV infection [7]. SOF can be used in combination with peg-IFN and RBV for 12 weeks, leading to SVR rates of 90% in patients with HCV GT1 infection, and with RBV alone for 12 weeks for GT2 as well as 24 weeks for GT3 [24–26]. IFN-free SOF based therapies of GT1 should always include a combination with other DAA. Further substances with this pan-GT DAA activity are currently under development, e.g. MK-3682 (formerly known as IDX21437), in a phase I/IIa study.

DAAs are considered pangenotypic when they

achieve high treatment efficacy across all six major HCV genotypes (9). Sofosbuvir/velpatasvir is an FDC of a pangenotypic NS5A inhibitor and sofosbuvir. It was approved both by the FDA and EMA in 2016. In clinical trials, it is associated with good efficacy in infections with genotypes 1–6, HIV/HCV coinfection, persons on opioid substitution therapy (OST) and persons with compensated or decompensated cirrhosis.

Sofosbuvir/velpatasvir/voxilaprevir is generally considered for use in the retreatment of HCV-infected persons who previously failed a DAA regimen however, in some HICs it is also registered for treatment-naive HCV-infected persons.

Glecaprevir/pibrentasvir is an FDC containing a pangenotypic NS3/4A protease inhibitor with a pangenotypic NS5A inhibitor that was approved by the FDA and EMA in 2017. In clinical trials, glecaprevir/pibrentasvir suggest good efficacy in infections with genotypes 1–6, compensated cirrhosis, including in persons with renal insufficiency and end-stage renal disease . It is contraindicated in persons with decompensated cirrhosis (Child–Pugh Class C).

A study in 4 academic centers in Taiwan showed that the overall SVR12 rate in patients receiving generic SOF in combination with RBV or NS5A inhibitors was excellent (95.4%) and was comparable to the response rates in patients receiving brand-name agents. The per-protocol SVR12 rate was 97.1% after excluding patients with non-virologic failure. Regarding safety, >99% of patients completed the scheduled treatment. Only 2 decompensated cirrhotic patients prematurely discontinued treatment due to spontaneous bacterial peritonitis, which were considered not related to DAA usage. In patients receiving SOF/RBV, infected with HCV-2, the SVR12 rate was (88.2%), whether extending the treatment to 16 weeks could achieve better response rates in HCV-2 cirrhotic patients needs further evaluation. The SVR12 rate of patients receiving generic SOF/LDV-based therapies was 93.5%, which was comparable to the response rates in patients receiving brand-name agents. About 66.5% of patients were treated by generic SOF/DCV or SOF/VEL. The SVR12 rates in patients receiving generic SOF/DCV and SOF/VEL-based therapies were excellent and were comparable to the phase III clinical trials and real-world reports. Of 23 decompensated cirrhotic patients receiving generic SOF/DCV or SOF/VEL with RBV for 12 weeks, or SOF/DCV or SOF/VEL without RBV for 24 weeks, all achieved SVR12, indicating these agents still had good therapeutic effects in critically ill patients. Furthermore, the response rates remained excellent in patients with unfavorable baseline characteristics. The study data indicated that generic SOF/DCV or SOF/VEL also had similar effectiveness to brand-name agents. Most patients had improving Child-Pugh class and MELD scores following treatment, implying that the mortality and morbidity can potentially be reduced in these very sick patients. In addition to the excellent safety profiles and effectiveness, the prices of generic SOF-based DAA therapies are about 1–2% of the brand-name agents. Based on these advantages, the use of generic SOF-based IFN-free DAA regimens may facilitate the mass treatment and play an important role in the elimination of HCV infection in the world, particularly in resource-constrained countries. Generic SOF-based IFN-free regimens achieved comparably excellent effectiveness and safety to the brand-name agents. These regimens may improve the care of HCV for patients with limited access to the expensive brand-name agents (2). The adverse effects of interferon (IFN)-based therapies, such as hematological toxicity and depression has not been well-documented. Third Department of Internal Medicine and Department of Endoscopy, of Nara Medical University, did a study were evaluated the efficacy and tolerability of various IFN-free treatment regimens in Japanese patients with HCV genotype-1 infection and evaluated the severity of depression symptoms using the Beck Depression Inventory-II (BDI-II) questionnaire .The results of the study show that various 12-week IFN-free treatment regimens were highly effective and tolerable in patients with HCV genotype-1 infection. Chronic HCV infection has a profound negative impact on mental health disorders, including depression. Patients with depression treated with DCV/ASV for 24 weeks had higher BDI-II scores at week 4, but lower scores at week 12 than at pretreatment in spite of the rapid decline of serum HCV levels. Ichikawa et al. demonstrated that 24-week DAA treatment eliminated HCV-RNA and improved psychologic distress. The 24-week DAA treatment would have temporary negative effects by leading to the development of anxiety over a long term therapy but would have also provided positive effects in the long term by yielding clinical benefits following HCV eradication. These findings reinforce the notion that the 12-week regimen was effective and safe for patients with HCV genotype-1 infection, including those with depression. Collectively, all four DAA regimens achieved similar high efficacy in Japanese patients with HCV genotype-1 infection. The 24-week DAA treatment had temporary negative impact on the mental health in patients with HCV infection. The BDI-II scores had significantly decreased following a 12-week regimen of SOF/LDV or EBR/GZR (4).

Conclusion

– IFN-free therapy with novel DAA regimens cure >90% of chronic HCV-infected patients.

– DAA regimens include NS5B nucleotide inhibitors, NS5B nonnucleoside inhibitors, NS5A replication complex inhibitors, and NS3/4A protease inhibitors.

– Depending on the stage of liver disease, HCV GT, and viral load, treatment duration varies between 8 and 24 weeks.

– DAA resistance has a minor influence on cure rates in first-line treatments but resistance testing should be performed before second-line therapies are initiated.

– Generic SOF-based IFN-free regimens achieved comparably excellent effectiveness and safety to the brand-name agents.

– The 24-week DAA treatment had temporary negative impact on the mental health in patients with HCV infection.

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