Lipa Katarzyna, Jabłońska Magdalena Julia, Kaczor Patryk, Leis Kamil, Kałużny Krystian, Gałązka Przemysław. Sofosbuvir as a drug in recurrent HCV therapy occurring after liver transplantation. Journal of Education, Health and Sport. 2018;8(9):628-642 eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1412333
http://ojs.ukw.edu.pl/index.php/johs/article/view/5950

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.08.2018. Revised: 18.08.2018. Accepted: 10.09.2018.

Sofosbuvir as a drug in recurrent HCV therapy occurring after liver transplantation

Katarzyna Lipa[1], Magdalena Julia Jabłońska[1], Patryk Kaczor[1*], Kamil Leis[1], Krystian Kałużny[2], Przemysław Gałązka[3]

[1]Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland
[2]Chair and Clinic of Rehabilitation, Faculty of Health Sciences, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland
[3]Department of General and Oncological Surgery for Children and Adolescents, Antoni Jurasz University Hospital No. 1 in Bydgoszcz, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-094 Bydgoszcz, Poland
*Corresponding author: Patryk Kaczor, ul. M. Curie Skłodowskiej 9 85-094 Bydgoszcz, Tel. 52/585 40 15, mail – patryk.kaczor97@gmail.com

Abstract

Sofosbuvir is a drug, which has been found useful in HCV (Hepatis C Virus) therapy. It replaced the previously used interferon, the applied of which has shown many side effects or lack of response to treatment. The usage of sofosbuvir with ribavirin shortens the time of treatment and minimizes the number of side effects. It is taken as a single dose of 400 mg for 12 or 24 weeks. The only place of activation of this prodrug is hepatocytes, where its active metabolite is formed (GS-461203). It should not be used together with P-glycoprotein inductors that can reduce the

efficiency of its action and with amiodarone, because application of both of them together slows down the heart rate. Numerous tests have demonstrated the effectiveness of sofosbuvir in the treatment of patients who have relapsed disease after liver transplantation. A high percentage of sustained virologic response obtained in all phases of clinical trials has proven the efficacy of sofosbuvir in combination with ribavirin or another HCV drug in the therapy of hepatitis C infection.

Keywords: sofosbuvir, Hepatis C Virus, liver transplant

Introduction

HCV (Hepatitis C Virus) is currently one of the main causes of chronic hepatitis in the world. It is estimated that around 160 million people are infected with this virus, most of which have not been diagnosed [1]. Sofosbuvir, known under a trade name Sovaldi® is a drug used to treat chronic hepatitis C [2]. It was developed in 2007 and approved for general sale in the United States in 2013 [3]. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America in 2016 recommended the use of sofosbuvir in combination with other drugs as a first-line therapy for the treatment of six genotypes of HCV (1, 2, 3, 4, 5, 6) and in some cases of second-line therapy [4]. Previously, hepatitis C was treated with interferon and ribavirin, which guaranteed less than 70% chance of cure (with sofosbuvir efficacy of 30-97% depending on virus genotype) and resulted in long-term therapy (6-12 months, sofosbuvir 12-24 weeks) with numerous side effects (more common than with sofosbuvir) such as nausea, diarrhoea, severe rash, anaemia, depression and fatigue [5, 6, 7, 8, 9].

Mechanism of action

Sofosbuvir is the NS5B inhibitor for HCV polymerase [10] necessary for virus replication. As a prodrug, it undergoes intracellular metabolism in hepatocytes forming a pharmacologically active analogue of uridine triphosphate GS-461203 (β-d-2'-deoxy-2'-α-fluoro-2’-β-C-methyluridine triphosphate), which is not present in plasma [9, 11]. The first stage of activation is the hydrolysis of the carboxylic ester, for which catepsin A (CatA) and to a lesser extent, carboxyl esterase (CES1) are responsible [12]. Hepatocytes are the only places where enzymes necessary to activate a prodrug are found [13]. Then, by eliminating phenol, the metabolite PSI-352707 is produced, from which the amino acid group is removed by a process catalyzed by

the nucleotide binding protein of histidine triad 1 (Hint1). The effect of Hint1 results in PSI-7411, a form of 5'-monophosphate, which can be phosphorylated to diphosphate (PSI-7410) by the kinase UMP-CMP and the active metabolite triphosphate (PSI-7409) by the nucleotide derivative of diphosphate [12, 13]. The active metabolite acts as a RNA HCV chain inhibitor via NS5B polymerase [14]. Sofosbuvir and its metabolites are not inhibitors of human isoenzymes UGT1A1 or CYP1A2, CYP3A4, CYP2C19, CYP2C9, CYP2D6, CYP2B6 and CYP2C8 [9, 14].

Characteristics

The drug is taken orally for 12 or 24 weeks, once a day at a dose of 400 mg [9]. The highest concentration is observed 0. 5-2 hours after administration, regardless of whether it is applied to a healthy or sick person and the dose received [9, 15]. The maximum level of the main metabolite sofosbuvir, GS-331007, [15] which is an inactive nucleoside formed in parallel pathways to form the active metabolite GS-461203 [9, 16] is found in plasma after 2-4 hours [15]. After a single dose of 400 mg of the drug, GS-331007 represented more than 90% of all metabolites formed [17]. Its half-life is 27 hours and that of sofosbuvir is 0. 4 hours [16].

The binding of sofosbuvir to plasma proteins in individuals, both healthy and with end-stage renal failure in ex vivo studies, was approximately 82-85%, while the metabolite GS-331007 was significantly lower [15].

The drug is excreted in 80% in urine, 14% in faeces and 2. 5% in exhaled air (using a single oral dose of 400 mg). The urine contains primarily GS-331007 (78%), and sofosbuvir is 3.5% [9, 15].

Interactions and side effects

Sofosbuvir as a substrate for P-glycoprotein [9], which mission is to transport medication from the intestinal epithelium back to its light [18], should not be used in combination with drugs which are strong and moderate inductors of this transporter in the intestine. The first group includes, among others, rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine and St. John's wort, while the second group includes, inter alia, modafinil and oxcarbazepine. All these drugs can reduce the therapeutic effect of sofosbuvir by lowering its concentration in plasma [9].

In patients treated with vitamin K antagonists, continuous monitoring of the international normalized ratio (INR) is recommended due to the possibility of changing liver function during sofosbuvir’s therapy [9].

Sofosbuvir, should not be used in combination with daclatasvir, ledipasvir or simeprevir with amiodarone, because it contributes to a slow heart rate, which was reported by the American Food and Drug Administration (FDA) in 2015 [16, 19].

A study by Kirby et al. showed that it is not necessary to adjust the doses of antiretroviral and sofosbuvir with their simultaneous use. With the application of tenofovir DF (TDF), emtricitabine (FTC) or efavirenz (EFV) the maximum concentration of sofosbuvir and its metabolite GS-331007 is reduced by 19% and 23% respectively, while with the application of rilpivirine (RPV) the concentration of sofosbuvir increases by 21%. Similarly, when used in the treatment of darunavir (DRV) or ritonavir (RTV), which inhibits the action of P-glycoprotein, the absorption of sofosbuvir increases [20, 21].

In the case of oral contraceptives, there is no need to correct the doses, either of sofosbuvir, ethinyl estradiol or norgestimate, when sofosbuvir is used concomitantly with one of these drugs, as sofosbuvir does not reduce the effectiveness of hormone therapy [9, 15].

The most common side effects are nausea, dizziness and headaches, shivers, fatigue, rash, back pain, irritability, anaemia and difficulties in falling asleep [16]. There is no data on symptoms occurring in the case of a sofosbuvir overdose. The maximum dose received by patients was 1200 mg and no adverse reactions other than those occurring at the standard dose of 400 mg or in placebo were observed [9].

Pregnancy and breast-feeding

It has not been established yet whether the drug is able to overcome the placenta barrier in the human body. Studies in rabbits and rats have shown that the metabolites of sofosbuvir are not only able to pass through the placenta, but also to enter the milk of these animals during lactation. It has not been proven, however, that taking this medicine causes death or inhibits the growth of embryos and foetuses [22]. The FDA (Food and Drug Administration) has systematized sofosbuvir when it was administered alone or in combination with ledipasvir to category B [22, 23] (studies on animals did not reveal any risk to the fetus, but appropriate studies were not performed in pregnant women [24]). However, in combination with ribavirin, it has been classified as X category [15] (taking this medicine causes significant disturbances in the development of the fetus in humans and animals [24]). Sofosbuvir therapy with ribavirin cannot be started until a negative pregnancy test has been performed. In addition, during and for 6 months after treatment, it is recommended to use two effective methods of contraception and to perform a pregnancy test once a month [25]. It has not been proven that sofosbuvir (alone

or in combination with ribavirin) is able to pass into breast milk, so it is not recommended to take it alone or together with ribavirin during breastfeeding [16, 22].

Sofosbuvir and transplants

Recurrent hepatitis C is a common complication after liver transplantation. A study by Forns et al. in 2014 showed that the use of sofosbuvir and ribavirin is effective in treatment of hepatitis C after grafting. This also applies to patients with decompensated cirrhosis and fibrosing cholestatic hepatitis (FCH) after graft. Sofosbuvir at a dose of 400 mg daily and ribavirin (depending on the clinical situation of the patient) were taken by patients for 24 weeks. A sustained virological response (SVR) occurred in 59% of subjects 12 weeks after the end of therapy (54 out of 92 analyzed) [26].

The first patient who did not use interferon for cure of HCV after transplantation was a 54-year-old man with cholestatic HCV (genotype 1b) and ascites, whose case was described in 2013. He was treated with sofosbuvir (400 mg daily) and daclatasvir (60 mg daily) for 24 weeks. Just after 4 weeks of medication, the levels of HCV RNA in the patient's serum were unnoticeable and the ascites receded. A sustained virological response occurred in a man 9 months after the end of treatment. The taken sofosbuvir and daclatasvir did not decrease the concentration of tacrolimus in the blood, obtained to prevent the rejection of the transplant, and its dose did not have to be modified either [27, 28]. In the study conducted by Sulkowski et al. in 2014 (phase II of clinical trials) the efficacy of both drugs in patients with genotype 1, 2 and 3 HCV was analyzed. For each genotype 44 patients were assigned and orally treated with 400 mg of sofosbuvir per day and 60 mg of daclatasvir per day (in some patients ribavirin was additionally used) for 24 weeks. In addition, 123 new patients with genotype 1 HCV were later admitted to the study with the same dosage regimen, the only change being different therapy duration (12 or 24 weeks). For all genotypes tested, maintenance of virological response was observed after treatment with sofosbuvir and daclatasvir, also in patients with previous resistance to treatment with boceprevir or telaprevir [29]. The ALLY-1 study from 2014 (stage III of clinical trials), in which patients with genotypes 1, 2, 3, 4, 6 HCV took part, confirmed the efficacy of sofosbuvir (400mg/day), daclatasvir (60mg/day) and ribavirin (600mg/day) in treating hepatitis C after graft of this organ [30].

Tests using sofosbuvir and ledipasvir also confirmed the effectiveness of therapy of chronic C hepatitis, which occurred in patients after transplantation. In the Kwok et al study, patients were treated with sofosbuvir (400mg / day) and ledipasvir (90mg / day) with ribavirin (400 or 1200 mg / day) or without, for a period of 8, 12 or 24 weeks. In 96% of subjects, regardless of HCV

genotype and duration of treatment, no virus was found after 12 weeks from the end of cure [31]. From January to August 2014, researchers from 34 centers in Europe, Australia, Canada and New Zealand tested the efficacy of sofosbuvir (400 mg per day), ledipasvir (90 mg per day) and ribavirin (600-1200 mg per day) for 12 or 24 weeks in patients with advanced cirrhosis after transplantation and without previous liver graft with genotype 1 or 4 HCV. In the subjects, the applied medication gave a high percentage of patients with sustained virological response after 12 weeks from the end of the examination, regardless of whether they had previously undergone surgery or not [32]. A multicenter, open-label study by Levitsky et al. also demonstrated the efficacy of perioperative care in patients with HCV genotype 1 who would receive liver from a non-HCV infected donor. The subjects obtained on the day of admission to the hospital ledipasvir (90mg) and sofosbuvir (400mg) and were treated with the same schedule for 4 weeks after the surgery. The results, despite the shorter treatment time than the standard (4 weeks instead of 12-24), were very satisfactory - 88% maintained the virological response. This confirmed the thesis put forward by the researchers that ledipasvir and sofosbuvir administered prevent recurrence of viral hepatitis in patients after the transplantation procedure [33].

Lawitz et al. conducted a study on patients with HCV genotype 1 from November 2011 to January 2014 at 23 centers in the United States (Phase II of the study), which were administered, after the grafting of the liver, sofosbuvir (400 mg per day) and simeprevir (150 mg per day) for 12 weeks (with or without ribavirin) or for 24 weeks (with or without ribavirin). In 92% of the subjects after 12 weeks there were a sustained virological response, which documented the effectiveness and safety of the use of sofosbuvir and simeprevir in the post-transplant cure of HCV [34].

Prevention of HCV recurrence after graft, through administration of sofosbuvir and ribavirin before operation, was analyzed by Curry et al. in 13 centers in the United States, New Zealand and Spain. Patients waiting for a grafting with HCV (without distinction between genotype) and cirrhosis received sofosbuvir in the standard dose and 1000 mg or 1200 mg ribavirin (depending on the patient's weight) before surgery for 48 weeks. Twelve weeks after a surgery, 70% of those who had an organ transplant had a virological response, 23% had a relapse and 7% died (3 people - 2 due to primary rejection and 1 due to hepatic artery thrombosis). This study showed that sofosbuvir in combination with ribavirin, administered before the procedure, give satisfactory results in preventing recurrent HCV after transplantation [35].

Clinical trials

Phase I clinical trial conducted in 2011-2012 in the United States and Puerto Rico, where sofosbuvir (PSI-7977) and PSI-352938 were used, checked whether the effectiveness of treatment of hepatitis C patients is the same as in patients infected with HCV without abnormal liver function. These tests were to show whether it is possible to include people with hepatic impairment and cirrhosis in the future. The patients (24) were divided into 6 groups: two groups included patients with class A according to the Child-Pugh score (5-6 points), one of them received 300 mg PSI-352938 per day and the other 400 mg of sofosbuvir for 7 days, two more groups with 7-9 points in Child-Pugh score (class B) obtained the same dose of medication for a week, as well as the last two groups assigned to class C of Child-Pugh score (10-15 points). However, the results of these studies have not been published [36].

Osinusi et al. in the open, randomized, I and II phase clinical trials checked the efficacy of sofosbuvir and ribavirin in HCV treatment. In phase I, 10 subjects with early or moderate degrees of Knodell histology activity index (HAI) (0-1) received sofosbuvir 400 mg and ribavirin in a dose dependent on the patient's weight for 24 weeks. The second phase was divided into two parts, in the first 25 patients obtained for 24 weeks sofosbuvir (400 mg) and ribavirin (1000 mg in people weighing less than 75 kg and 1200 mg in patients weighing more than 75 kg), and 25 subjects took sofosbuvir in a dose 400 mg and ribavirin in the lower dose (600 mg) for 24 weeks (second part of the study). In the second phase, patients were included regardless of the degree of liver fibrosis. The lack of viruses in the body was found in 90% of patients from the first group of 10 patients, 68% from the second group and 48% from the last group [37, 38].

From January 2010 to August 2011, Rodriguez-Torres M et al. analyzed the efficacy of sofosbuvir with peginterferon and ribavirin in the initial stage of phase II of clinical trial. Patients (64 individuals) with HCV genotype 1, who had not been treated before, were randomly assigned to 4 groups. They received orally, apart from peginterferon and ribavirin, sofosbuvir at a dose of 100 mg (first group), at a dose of 200 mg (second group), 300 mg (third group), and the last one obtained a placebo. The treatment lasted 28 days, and after it, for the next 44 weeks they took peginterferon and ribavirin. Patients who took sofosbuvir had a greater reduction of HCV RNA and a faster virological response than those receiving placebo. The sustained virological response after 24 weeks from the end of therapy was equal to 56%, 83%, 80% and 43%, for 100 mg, 200 mg, 400 mg of sofosbuvir and placebo, respectively. In addition, due to the higher number of people with relapse of the disease at a dose of 100 mg than 200 and

400 mg, it was decided that in phase IIb further analysis will be subjected to sofosbuvir in doses of 200 and 400 mg [39].

In the second phase of clinical trials, PROTON, Lawitz E et al. study evaluated the efficacy of sofosbuvir therapy in previously untreated patients with HCV genotypes 1, 2 and 3. The two-cohort, double-blind study involved 147 subjects (122 in cohort A and 25 in cohort B). Cohort A included patients with HCV genotype 1, who were divided into 3 groups (2: 2: 1 ratio) - for 12 weeks they took peginterferon together with sofosbuvir (180 μg per week) and ribavirin (1000 or 1200 mg per day)) - the first group received 200 mg of sofosbuvir, the second 400 mg, while the third one took placebo. Then for the next 12 or 36 weeks they assumed peginterferon and ribavirin. In cohort B, all patients obtained 400 mg of sofosbuvir, peginterferon and ribavirin for over a period of 12 weeks. Twelve weeks after the end of treatment, HCV RNA was undetectable at a dose of 200 mg sofosbuvir in 90% of subjects, in 91% of those taking 400 mg of sofosbuvir, in 58% of placebo and 92% of cohort B (400 mg sofosbuvir) [40].

Kowdley et al. in an open, randomized ATOMIC study (phase II) from 2011-2012 analyzed 316 patients from 42 centers in the USA and Puerto Rico with diagnosed HCV (genotype 1, 4, 5 and 6). Patients with genotype 1 were divided into three cohorts: cohort A took 400mg of sofosbuvir and peginterferon with ribavirin for 12 weeks, cohort B received the same for 24 weeks (all other patients with other HCV genotypes, who took part in the tests were also included in cohort B). The last group (cohort C) obtained the same dose of sofosbuvir, peginterferon and ribavirin for 12 weeks, and for the next 12 weeks they got either sofosbuvir alone or in combination with ribavirin. The gained results did not show any difference in sustained virological response after 24 weeks from the end of the study in all cohorts. This indicated the lack of additional benefits from the prolongation of the duration of sofosbuvir therapy, which should be confirmed in the third phase of the study [41].

Gane et al. in the ELECTRON study, which was divided into 5 parts, was aimed to analyze the necessity of administering interferon in combination therapy with sofosbuvir. Forty HCV-infected with genotypes 2 or 3, who had not been treated before were divided into 4 groups (1: 1: 1: 1). All patients in 4 groups were given 400 mg sofosbuvir and ribavirin once daily for 12 weeks. Additionally, patients from 3 groups received peginterferon alfa-2a for 4, 8 or 12 weeks. In two additional groups also comprised of patients with genotype 2 or 3 and without prior treatment, either alone sofosbuvir was used in 12-week therapy, or for 8 weeks sofosbuvir with ribavirin and peginterferon alfa-2a (10 people). In patients with HCV genotype 1, sofosbuvir and ribavirin (12 weeks) were used - 25 patients in this group had not been treated before and

10 had not responded to previous cures. In 100% of the subjects from the first 4 groups after 24 weeks HCV was not detected, regardless of the duration of therapy and whether peginterferon was used or not. The results of two additional groups (genotypes 2 and 3), who received sofosbuvir with ribavirin and interferon, were the same as in the previous described studies (100% sustained viral response after 24 weeks), whereas in the case of sofosbuvir therapy no viruses were found in 60 % of patients. Sicks with HCV genotype 1 had a sustained virological response of 84% in previously untreated and 10% in those with a history of failure in treatment. The study proved that sofosbuvir with ribavirin used for 12 weeks is effective in patients with genotype 1, 2 or 3 HCV who had not been treated before [42]. In the subsequent stages of the ELECTRON study, Gane et al. evaluated the effectiveness of cure of patients with HCV genotype 1 with sofosbuvir and ledipasvir or GS5669 - non-nucleoside inhibitor of NS5B. In the therapy took part 113 people, who had not been cured before or did not respond to previous medication. In 34 patients (25 previously untreated and 9 without effective treatment) sofosbuvir (400 mg daily), ledipasvir (90 mg per day) and ribavirin were used for 12 weeks. Therapy of 35 patients (25 without prior medication and 10 with unsuccessful cure) was also continued for 12 weeks. They got sofosbuvir, ribavirin and GS-9669 (500 mg daily). People with cirrhosis were randomly assigned to 2 groups - 9 people obtained sofosbuvir, ledipasvir and ribavirin, 10 were treated with ledipasvir and sofosbuvir. Sofosbuvir, ledipasvir and ribavirin also received 25 patients in 6 weeks of therapy who had not previously been cured with HCV. The results of sustained viral response after 12 weeks have shown that sofosbuvir together with another antiviral drug is effective in the medication of HCV with genotype 1 in patients previously untreated or without the success of previous therapies [43].

The LONESTAR study (Phase II) by Lawitz et al. tested the effectiveness of hepatitis C treatment without or with ribavirin at fixed doses of sofosbuvir and ledipasvir. The try consisted of 100 people with HCV genotype 1, who had not been treated before, or in whom therapy with other HCV inhibitors did not provide the results, were administered sofosbuvir in the standard dose and ledipasvir (90 mg / day) without or with ribavirin. In cohort A, there were 60 patients previously untreated with no cirrhosis, divided into 3 groups: the first one received for 8 weeks sofosbuvir and ledipasvir, the second for the same time received additional ribavirin, while the third one sofosbuvir and ledipasvir for 12 weeks. In cohort B, there were patients with or without cirrhosis who had been previously cured with failure. They were assigned to two groups, one of them for 12 weeks was treated with sofosbuvir and ledipasvir (group 4), while the other group obtained ribavirin (group 5) under the same scheme. The results showed that established doses for sofosbuvir and ledipasvir (with or without ribavirin) are able to cure HCV

patients with genotype 1 with almost 100% efficacy (regardless of the duration of therapy, with ribavirin it was always 100% tested with sustained virological response after 12 weeks from the end of treatment and 95% in the absence of ribavirin). Previous failures of medication and cirrhosis of the liver did not affect the success of the cure. Therefore, further clinical trials are necessary to develop the best duration of therapy and the necessity of ribavirin [44].

In all phase III studies, the dose of sofosbuvir received by patients was 400 mg daily, while the dose of ribavirin depended on the patient's weight [45]. Lawitz et al. conducted two studies in patients who had not previously been treated for HCV. In the first group of 327 patients with HCV genotype 1, 4, 5 and 6 (of which 98% had genotype 1 or 4), sofosbuvir, peginterferon alfa-2a and ribavirin (NEUTRINO study) were administered for 12 weeks. After 12 weeks, no viruses were found in 90% of ills. In the second trial, 499 patients with genotype 2 or 3 HCV got for 12 weeks sofosbuvir plus ribavirin or ribavirin with peginterferon alfa-2a for 24 weeks (FISSION). The sustained virological response after 12 weeks of treatment was in both groups at the same level (67%), however the difference was noticeable depending on the HCV genotype (for genotype 3 SVR12 was 56%, while for genotype 2 SVR12 was equal to 97%) and whether the patients suffered from cirrhosis or not (47% to 72%) [8].

Jacobson et al. confirmed the efficacy presented in Phase II of the therapy with sofosbuvir in patients with HCV 2 or 3 genotype who were unable to use peginterferon (POSITRON), or had not been responded to treatment with prior use (FUSION). Two randomized trials were performed at POSITRON, the first of which included patients who could not use peginterferon in the therapy, so for 12 weeks, 207 of them got sofosbuvir and ribavirin, and 71 sofosbuvir with placebo. FUSION included individuals who had not previously responded to peginterferon cure - 103 obtained sofosbuvir and ribavirin for 12 weeks, while 98 patients underwent, with the same scheme, 16 weeks of medication. In the POSITRON study, the sustained virological response in subjects who received sofosbuvir with ribavirin was 78% compared to 0% in placebo-treated people. In patients previously cured with peginterferon, the response rate was at the level of 50% for a 12-week treatment and 73% for a 16-week medication. This confirmed that the therapy with sofosbuvir and ribavirin for 12 or 16 weeks is effective in these patients [46].

Summary

Many clinical trials have proven that HCV therapy with sofosbuvir is effective. The shortening of the treatment time in comparison with the previously used interferon is its advantage. Also, a small number of side effects, which occur less frequently than in comparison with interferon

and a small number of drugs with which it interacts is an undoubted benefit. The tests carried out show that sofosbuvir is a good remedy for the cure of recurrent hepatitis C after transplantation.

References:

1. Pawlotsky, Jean-Michel, et al. "EASL recommendations on treatment of hepatitis C 2015." J hepatol 63.1 (2015): 199-236.
2. https://www.hepatitisc.uw.edu/page/treatment/drugs/sofosbuvir-drug
3. Food, F. D. A. U. S. "Drug Administration. FDA news release. FDA approves Epclusa for treatment of chronic hepatitis C virus infection [press release][Internet]. Silver Spring: United States Food and Drug Administration; 2016 [cited 2017 Jan 26]."
4. https://www.hcvguidelines.org/sites/default/files/HCV-Guidance_October_2016_a.pdf
5. https://bazalekow.mp.pl/leki/doctor_subst.html?id=3641
6. Poynard, Thierry, et al. "Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration." Hepatology 24.4 (1996): 778-789.
7. https://www.wsj.com/articles/SB10001424127887323293704578330712442353712
8. Lawitz, Eric, et al. "Sofosbuvir for previously untreated chronic hepatitis C infection." New England Journal of Medicine 368.20 (2013): 1878-1887.
9. https://www.medicines.org.uk/emc/medicine/28539
10. Pol, Stanislas, Marion Corouge, and Anaïs Vallet-Pichard. "Daclatasvir–sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life." Hepatic medicine: evidence and research 8 (2016): 21-26
11. Fung, Amy, et al. "Efficiency of incorporation and chain termination determines the inhibition potency of 2′-modified nucleotide analogs against HCV polymerase." Antimicrobial agents and chemotherapy(2014): AAC-02666.; doi: 10.1128/AAC.02666-14
12. Murakami, Eisuke, et al. "Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977." Journal of biological chemistry (2010): jbc-M110.; doi: 10.1074/jbc.M110.161802
13. Bhatia, Harmeet Kaur, et al. "Sofosbuvir: a novel treatment option for chronic hepatitis C infection." Journal of pharmacology & pharmacotherapeutics5.4 (2014): 278-284
14. Cuenca-Lopez, Francisca, Antonio Rivero, and Antonio Rivero-Juárez. "Pharmacokinetics and pharmacodynamics of sofosbuvir and ledipasvir for the treatment of hepatitis C." Expert opinion on drug metabolism & toxicology 13.1 (2017): 105-112.
15. Kirby, Brian J., et al. "Pharmacokinetic, pharmacodynamic, and drug-interaction profile of the hepatitis C virus NS5B polymerase inhibitor sofosbuvir." Clinical pharmacokinetics 54.7 (2015): 677-690.
16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s002lbl.pdf

17. Kirby, Brian, et al. "Population Pharmacokinetics of Sofosbuvir and Its Major Metabolite (gs-331007) in Healthy and HCV infected Adult Subjects: 1106." Hepatology 58 (2013): 746A-747A.

18. Sokolowska, J., K. Urbanska, and D. Klosinska. "Rola glikoproteiny P w warunkach fizjologicznych iw stanach patologicznych. Część I. Budowa chemiczna i biologiczna rola glikoproteiny P." Życie Weterynaryjne 89.11 (2014).

19. Back, David J., and David M. Burger. "Interaction between amiodarone and sofosbuvir-based treatment for hepatitis C virus infection: potential mechanisms and lessons to be learned." Gastroenterology 149.6 (2015): 1315-1317.

20. Kirby, B., et al. "GS-7977 & HIV ARTs PK—no clinically significant pharmacokinetic interactions between sofosbuvir (GS-7977) and HIV antiretrovirals atripla, rilpivirine, darunavir/ritonavir, or raltegravir in healthy volunteers." 63rd Annual Meeting of the American Association for the Study of Liver Diseases. 2012.

21. Karageorgopoulos, Drosos E., et al. "Drug interactions between antiretrovirals and new or emerging direct-acting antivirals in HIV/hepatitis C virus coinfection." Current opinion in infectious diseases 27.1 (2014): 36-45.

22. Spera, Anna Maria, et al. "Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women?." World journal of hepatology 8.12 (2016): 557-565

23. Hussar, Daniel A., and Zhimeng Jenny Jin. "New drugs: simeprevir, sofosbuvir, and dolutegravir sodium." Journal of the American Pharmacists Association 54.2 (2014): 202-207.

24. https://www.drugs.com/pregnancy-categories.html#previous

25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21511slr002_copegus_lbl.pdf

26. Forns, Xavier, et al. "Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation." Hepatology 61.5 (2015): 1485-1494.

27. Fontana, R. J., et al. "Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C." American Journal of Transplantation 13.6 (2013): 1601-1605.

28. https://bazalekow.mp.pl/leki/doctor_subst.html?id=2080

29. Sulkowski, Mark S., et al. "Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection." New England Journal of Medicine370.3 (2014): 211-221.

30. Poordad, Fred, et al. "Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence." Hepatology 63.5 (2016): 1493-1505.

31. Kwok, Ryan M., et al. "Sofosbuvir plus ledispasvir for recurrent hepatitis C in liver transplant recipients." Liver Transplantation 22.11 (2016): 1536-1543.
32. Manns, Michael, et al. "Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial." The Lancet Infectious Diseases 16.6 (2016): 685-697.
33. Levitsky, Josh, et al. "Perioperative ledipasvir–sofosbuvir for HCV in liver-transplant recipients." New England Journal of Medicine 375.21 (2016): 2106-2108.
34. Lawitz, Eric, et al. "Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study." The Lancet 384.9956 (2014): 1756-1765.
35. Curry, Michael P., et al. "Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study." Gastroenterology 148.1 (2015): 100-107.
36. https://clinicaltrials.gov/ct2/show/record/NCT01497327?term=sofosbuvir&phase=04&draw=3&rank=17
37. Osinusi, Anuoluwapo, et al. "Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial." Jama 310.8 (2013): 804-811.
38. https://clinicaltrials.gov/ct2/show/results/NCT01441180?sect=X01256
39. Rodriguez-Torres, Maribel, et al. "Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial." Journal of hepatology 58.4 (2013): 663-668.
40. Lawitz, Eric, et al. "Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial." The Lancet infectious diseases 13.5 (2013): 401-408.
41. Kowdley, Kris V., et al. "Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial." The Lancet 381.9883 (2013): 2100-2107.
42. Gane, Edward J., et al. "Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C." New England Journal of Medicine 368.1 (2013): 34-44.
43. Gane, Edward J., et al. "Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection." Gastroenterology 146.3 (2014): 736-743.

44. Lawitz, Eric, et al. "Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial." The Lancet 383.9916 (2014): 515-523.

45. Stedman, Catherine. "Sofosbuvir, a NS5B polymerase inhibitor in the treatment of hepatitis C: a review of its clinical potential." Therapeutic advances in gastroenterology 7.3 (2014): 131-140.

46. Jacobson, Ira M., et al. "Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options." New England Journal of Medicine 368.20 (2013): 1867-1877.