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Review Article

SOFOSBUVIR: TREATMENT OF CHRONIC HEPATITIS C AND THE MAIN TRENDS IN PATENT PROTECTION

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ABSTRACT

The purpose of the study was to analyze and systematize the literature data on the benefit/risk ratio of sofosbuvir administration in the treatment of patients with chronic hepatitis C and the main trends in its patent protection. Studies were conducted using databases on the Internet: Ukrainian patent office, the European patent office, the US patent office, the Food and drug administration, European Medicines Agency (EMEA), State enterprise "The State Expert Center" of the Ministry of Health of Ukraine. It has used retrospective, logical, systematic and analytical methods. Data from clinical studies abroad and meta-analyses indicate that sofosbuvir is one of the most promising drugs for the treatment of chronic HCV infection. Its indisputable advantages are that this drug can be used with different genotypes of the virus, decompensated liver function, it is well tolerated. Sofosbuvir has an improved safety profile and a low probability of viral resistance. The high cost of sofosbuvir is due to the powerful patent protection. As mechanisms for working with patent barriers, it is recommended to use the flexible mechanisms of the TRIPS Agreement: the grant of compulsory licenses, the implementation of parallel imports, the tightening of the criteria for patentability (prohibition of patenting new forms that do not improve therapeutic efficacy).

Keywords: Sofosbuvir, Patent, Chronic hepatitis C, TRIPS

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INTRODUCTION

According to World Health Organization, morbidity and mortality associated with hepatitis C virus (HCV) infection continue to increase worldwide. Each year about 700,000 people die from HCV-related complications, including liver cirrhosis and hepatocellular carcinoma [1-6]. For Ukraine, the problem of HCV infection is really not only medically, but also socio-economically important. In Ukraine, infection with the hepatitis C virus of people over the age of 15 reaches 9% and up to 11,000 people die from its effects every year [7, 8]. According to the results of selective monitoring of risk groups, the level of HCV infection among some of them is much higher than the world average rates and reaches 40–60%. It should be noted that thanks to scientific breakthroughs towards the treatment of HCV infection, significant progress has been made in the treatment of this pathology and in fact, chronic hepatitis C has been transferred to the category of fully curable diseases.

Until recently, in Ukraine, the combination of pegylated interferon with ribavirin during 48-56 w was considered to be the recognized standard of therapy for this pathology. The effectiveness of this treatment was approximately 50%, that is, only half of the patients undergoing therapy had a chance of cure. But, in almost all cases this therapy was a peculiar kind of trial because of side effects, namely the "flu-like syndrome", which accompanied the patient during the entire course of therapy [7].

Taking into account international recommendations, as well as proven high efficacy and favorable safety profile of direct-acting antiviral agents (DAAs) in the treatment of chronic HCV, the Unified clinical protocol on primary, secondary, tertiary care "Viral hepatitis C in adults" was updated by Order of the Ministry of Health of Ukraine dated July 18, 2016 No. 729. The HCV treatment regimens of all genotypes were revised in the updated document.

There is no doubt that effective antiviral therapy leading to the eradication of HCV infection reduces the risk of progression of hepatic and extrahepatic HCV infection manifestations, especially if the treatment is carried out before the formation of liver cirrhosis [9-17].

At least 6 genotypes and dozens of subgenotypes of HCV, the distribution of which differs in different countries of the world, are currently described. In Russia, the United States, Europe and some other countries, the most common virus is genotype 1 (HCV-1), while HCV-3 is the second most common (22-30% of patients) [18-20].

As a result, interferon-free regimens with the use of DAAs were included in the treatment regimens of patients infected with HCV: sofosbuvir+ribavirin; sofosbuvir/ledipasvir; sofosbuvir+simeprevir; ombitasvir/paritaprevir/ritonavir and dasabuvir [21].

The purpose of the study was to analyze and systematize the literature data on the benefit/risk ratio of sofosbuvir administration in the treatment of patients with chronic hepatitis C and the main trends in its patent protection.

MATERIALS AND METHODS

Studies were conducted using databases on the Internet: Ukrainian patent office, the European patent office, the US patent office, the Food and drug administration, European Medicines Agency (EMEA), State enterprise "The State Expert Center" of the Ministry of Health of Ukraine. It has used retrospective, logical, systematic and analytical methods.

RESULTS AND DISCUSSION

The recommendations of the World Health Organization [22], the European Association for the Study of the Liver (EASL) [23] and the American Association for the Study of Liver Diseases (AASLD/The Infectious Diseases Society of America (IDSA), which consider current approaches to the treatment of chronic hepatitis C were published. All these recommendations proposed to use regimens that include sofosbuvir as one of the main regimens of antiviral therapy for chronic hepatitis [24].

Sofosbuvir is a nucleotide pan-genotypic inhibitor of the main replicative enzyme, the RNA-dependent RNA polymerase of the NS5B region of HCV. Sofosbuvir is a prodrug that, during intracellular metabolism, is transformed into a pharmacologically active analogue of uridine triphosphate. The standard dose of sofosbuvir is one 400 mg pill, which is taken as a single piece after a meal. After administration, sofosbuvir is rapidly absorbed. Sofosbuvir (mainly in the form of an inactive metabolite leaving hepatocytes after dephosphorylation) is characterized by an active

secretion of the renal tubules (80%). Sofosbuvir can be prescribed in a full dose only for mild and moderate renal impairment, while its use is not recommended in patients with severe renal insufficiency (glomerular filtration rate<30 ml/min/1.73 m^2) and in patients receiving treatment hemodialysis [25-27].

Although in case of moderate and severe hepatic insufficiency, the area under the concentration curve of sofosbuvir increases by 126% and 143%, and the active metabolite increases by 18% and 9%, respectively, nevertheless, sofosbuvir can be administered in full dose for any degree of hepatic failure.

Sofosbuvir has activity against all known HCV genotypes, has a high resistance barrier and the favorable safety profile [28]. Most adverse events observed in the clinical trials of sofosbuvir are associated with the simultaneous use of pegylated interferon and (or) ribavirin.

The efficacy and safety of sofosbuvir in patients with different HCV genotypes and various combinations of drugs were studied in large, well-designed clinical studies of the II and III phase (NEUTRINO [29], PROTON [30], ELECTRON [31], ATOMIC [32], COSMOS [33], FUSION [34], FISSION [29], NUCLEAR [35], POSITRON [34]) and systematized by Harmeet KB *et al.* [36]. In clinical studies of the II phase, it was found that the most effective dose of sofosbuvir is 400 mg with the duration of treatment from 12 to 24 w in various combinations with pegylated interferon and ribavirin. Similar results were obtained in numerous clinical studies of the III phase. Research results indicate a good safety profile of sofosbuvir. In its application, there was only a slight decrease in hemoglobin level and a much lower overall incidence of side effects compared with pegylated interferon-based regimens. The most frequently reported side effects were a headache, insomnia, general weakness, nausea, dizziness, pruritus, upper respiratory tract infections, skin rash, back pain, anemia grade 1, lymphopenia grade 4. While taking sofosbuvir, no cases of neutropenia, thrombocytopenia, or other serious side effects have been reported. In the groups of patients who received monotherapy, the only side effects that were likely to be associated with sofosbuvir were nausea and general weakness. Compared to a pegylated interferon-based regimen, tolerability of sofosbuvir monotherapy was significantly better. The data obtained indicate the efficacy and safety of sofosbuvir.

Table 1: Meta-analysis of the effectiveness and safety of sofosbuvir

Study	Results
1	2
Meta-analysis of six trials (2346 patients; 1625 treated with sofosbuvir)	It has not established an increased risk of cardiac outcomes, including arrhythmias (and bradycardia), among sofosbuvir-treated patients [38].
Meta-analysis of six randomized trials (n=1427 patients)	It has showed that the 12-week regimen of sofosbuvir plus velpatasvir was highly effective in HCV patients, including those with cirrhosis and former treatment experience. Except for genotype-3, adding ribavirin was not associated with significant improvements in SVR12 rates [39].
Meta-analysis of 16 trials (n=885 patients)	It has evaluated safety and efficacy of different combinations of direct-acting antivirals (DAAs: Sofosbuvir/ledipasvir (SOF/lDV), Paritaprevir/Ritonavir/Ombitasivir/Dasabuvir (PrOD), Daclatasvir (DCV)/Simeprevir (SMV)±Ribavirin (RBV) and SOF/SMV±RBV, Asunaprevir/Daclatavir (ASV/DCV)) in 885 liver transplant recipients with genotype 1 HCV) has carried out. It has established that DAA treatment is highly effective and well tolerated in liver transplant recipients with recurrent genotype 1 HCV infection [40].
Meta-analysis of 15 studies (4230 patients)	It has established that sofosbuvir+ribavirin for 24 w is the most widely used and generally well-tolerated DAA therapy in Asia. However, its effectiveness is not optimal in chronic hepatitis C (Genotype 3) patients with cirrhosis [41].
Meta-analysis of 7 studies (n = 1167 co-infected patients)	It has evaluated efficacy and safety of sofosbuvir-containing regimens in patients co-infected with chronic hepatitis C virus and human immunodeficiency virus. The results of this study showed that the treatment response of sofosbuvir-containing regimens in patients co-infected with HIV and HCV was satisfied. Attention should be paid to the high rates of adverse events [42].
Meta-analysis of 41 studies (n = 8574 patients)	All oral direct-acting antiviral (daclatasvir/asunaprevir, ledipasvir/sofosbuvir±ribavirin) regimens treatment of HCV GT1 resulted in high cure rates in Asian patients in routine clinical practice setting including elderly patients and those with end-stage renal disease [43].
Review of data of 3311 patients	It has established that the optimal therapeutic regimen for patients with HCV genotype 3 appears to be the combination sofosbuvir/daclatasvir, administered for 12 w without the use of RBV in non-cirrhotic patients. In cirrhotics the meta-analytic approach suggests extending therapy to 24 w [44].
8 studies (n =1892 patients)	The combination of sofosbuvir and ledipasvir achieved high sustained virological response rates (>90%) in both cirrhotic and non-cirrhotic patients with HCV genotype-1. The addition of ribavirin to this regimen did not significantly increase the sustained virological response rates [45].
7 studies (n = 379 patients)	Sofosbuvir+daclatasvir±ribavirin, regimen is of high efficacy and tolerability in liver transplant recipients with HCV infection [46].
10 studies (n =2248 patients)	The interferon-free regimen of sofosbuvir/ledipasvir for 12 or 24 w with or without ribavirin is highly effective for treatment of patient's withHCV genotype 1 infection [47].
1	**2**
7 studies (n =2626 patients)	Ledipasvir-sofosbuvir based therapy is a safe and effective treatment for patients with genotype 1 HCV. The addition of ribavirin to ledipasvir-sofosbuvir may increase toxicity without achieving improved efficacy. Large-scale and high-quality clinical research is still needed to confirm the results [48].
12 studies (n =994 patients)	Ledipasvir+sofosbuvir-based treatment is highly effective and well tolerated in liver transplant recipients with HCV reinfection [49].
7 studies (n =2601 patients)	The 12-week or 24-week sofosbuvir+ledipasvir regimen with a low incidence of adverse events is as effective and well tolerated as the sofosbuvir+ledipasvir+ribavirin regimen for the treatment of patients with chronic HCV genotype 1 infection [50].
9 studies (n =325 patients)	Simeprevir+sofosbuvir±ribavirin is safe and effective in recipients with liver transplant with HCV-1 infection [51].
27 studies (n =3415 patients)	Regimens containing sofosbuvir and velpatasvir to be the best option for patients with HCV genotype 3 infections. Analyses indicated that ribavirin significantly increases SVR rates and should be considered if tolerated [52].
18 studies (n =2975 patients)	The sofosbuvir-containing regimens in patients with HCV genotype 2 infection have better efficacy than in patients with HCV genotype 3 infections [53].

For further conducting pharmacokinetics studies and therapeutic drug monitoring it has developed a simple, accurate, precise, linear, rugged and rapid RP-HPLC method for quantitative estimation of sofosbuvir in human plasma [37].

Although numerous placebo-controlled studies of sofosbuvir are important evidence of its efficacy, there is a higher degree of evidence of its clinical benefits. The recognized standard of evidence-based medicine is a meta-analysis of the results of numerous studies. These sofosbuvir meta-analysis data are given in table 1.

Thus, the existing evidence base suggests that the use of sofosbuvir is effective and safe in patients in course of the treatment of viral hepatitis C, although the risk of side effects, such as fatigue, headache and nausea, cannot be totally excluded. Their severity increases with combination therapy with interferon and other antiviral drugs [54, 55].

Table 2: Analysis of patent protection of sofosbuvir and its combinations in the USA

Active pharmaceutical ingredient, trademark; dosage form	Patent No	Patent Expiration
1	2	3
sofosbuvir; SOVALDI; **Table**t; oral, 400 mg	7964580 8334270 8580765 8618076 8633309 8889159 9085573 9284342 9549941	03/26/2029 03/21/2028 03/21/2028 12/11/2030 03/26/2029 03/26/2029 03/21/2028 09/13/2030 03/26/2029
ledipasvir, sofosbuvir; HARVONI; **Table**t oral, 90 mg, 400 mg	10039779 7964580 8088368 8273341 8334270 8580765 8618076 8633309 8735372 8822430 8841278 8889159 9085573 9284342 9393256 9511056	01/30/2034 03/26/2029 05/12/2030 05/12/2030 03/21/2028 03/21/2028 12/11/2030 03/26/2029 03/21/2028 05/12/2030 05/12/2030 03/26/2029 03/21/2028 09/13/2030 09/14/2032 05/12/2030
sofosbuvir, velpatasvir; EPCLUSA; **Table**t; oral, 400 mg; 100 mg	10086011 7964580 8334270 8575135 8580765 8618076 8633309 8735372 8889159 8921341 8940718 9085573 9284342 9757406	01/30/2034 03/26/2029 03/21/2028 11/16/2032 03/21/2028 12/11/2030 03/26/2029 03/21/2028 03/26/2029 11/16/2032 11/16/2032 03/21/2028 09/13/2030 01/30/2034

1	**2**	**3**
sofosbuvir, velpatasvir, voxilaprevir; VOSEVI; **Table**t; oral, 400 mg; 100 mg; 100 mg	7964580 8334270 8575135 8580765 8618076 8633309 8735372 8889159 8921341 8940718 9085573 9284342 9296782 9585906 9868745	03/26/2029 03/21/2028 11/05/2033 03/21/2028 12/11/2030 03/26/2029 03/21/2028 03/26/2029 11/16/2032 11/16/2032 03/21/2028 09/13/2030 07/17/2034 03/21/2028 11/16/2032

It should be noted that sofosbuvir not only potentially provides a cure but challenges health care systems [56-63].

Access to innovative drugs and diagnostics is an important element in the control and treatment of hepatitis C infection. The prices requested for the new hepatitis C drugs, in particular, the direct-acting antivirals as sofosbuvir, are unsustainable for most countries' health budgets. These prices may deprive thousands of patients of a curative treatment. Consequently, it remains accessible only to the most severely ill patients, in many countries these patients are with hepatic fibrosis F3A4, and early stages are not treated. Hence, this transmissible disease will continue to drive new infections.

As of 2016, a 12-week course of sofosbuvir treatment costs about US$84,000 in the United States, US$53,000 in the United Kingdom, US$45,000 in Canada, and about US$500 in India [64-66].

The high cost of sofobusfir is related to its patent protection. The analysis of sofobusfir patenting revealed its powerful patent protection (table 2). The substance is protected by several patents in many countries. The expiration of a number of patents for sofosbuvir falls on the years of 2028-2034. This allows the pharmaceutical company, Gilead Sciences INC, to have a monopoly for the sale over a long period and improve their commercial prospects.

On 15 September 2014 Gilead Sciences INC signed licensing agreements with seven Indian generic manufacturers (Cadila, Cipla, Hetero, Mylan, Ranbaxy, Sequent and Strides Arcolab), allowing these companies to manufacture sofosbuvir in India and sell it in 91 low-and-middle-income countries. Generic companies pay 7% royalties and are free to set their own prices but have to produce or buy the active pharmaceutical ingredient in India. One company was quoted with an entry price of around US$ 300. One nongovernmental organization expects entry prices of US$ 400 per 12-week course and in the medium term a reduction to around US$ 135. Nevertheless, these generic products–which may become available within 12–18 mo–can only be used in the 91 countries listed, and the agreement only covers four countries in Europe: Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. Countries that are not included can negotiate price or issue compulsory licenses to access the Indian generic versions [64].

In March, 2017 the Patent EP 2604620 (Modified fluorinated nucleoside analogues) was challenged by "European Public Health Alliance", "Doctors Without Borders", "Doctors of the World" and several more international organizations [67].

On 13 September 2018 the European Patent Office (EPO) ruled in favour of the pharmaceutical company Gilead and maintained the company's patent on hepatitis C drug sofosbuvir. The patent, however, is maintained in an amended form. Civil society involved in the case expressed dismay over the outcome and its potential effect on European drug prices.

According to report of the world community advisory board on HCV generics and diagnostics other sofosbuvir patent oppositions in the world are given in table 3 [68].

Analysis of the range of sofosbuvir and management of the intellectual property in Ukraine is given in the table 4.

The problem of viral hepatitis is common to many countries of the world, and Ukraine is no exception. For the combined interferon-free regimens recommended for the treatment of patients with different HCV genotypes and at the same time available in Ukraine are sofosbuvir+ledipasvir; paritaprevir+ombitasvir+dasabuvir+ ritonavir; ombitasvir+paritprevir+ritonavir, sofosbuvir+simeprevir.

At the same time, the recommendations of EASL 2016 allow for the use of a combination of ledipasvir+sofosbuvir in patients with HCV 1st genotype (any subtype) without cirrhosis and past treatment experience in the abbreviated regime–for an 8-week course. In 2016, when sofosbuvir was added to the treatment regimen, the frequency of achieving a sustained virological response 12 w after the end of therapy (at least 95% of cases) was 95.2%.

Table 3: Sofosbuvir patent oppositions (according to report of the world community advisory board on HCV generics and diagnostics [68])

Patent opposed	Patent international publication number, title of patent	Country or region	Opponent (civil society only)	Year	Challenge status
Sofosbuvir (prodrug)	WO2008121634 "Nucleoside phosphoramidate prodrugs"	Argentina	FGEP	2015	Under examination
		China	I-MAK	2015	Patent rejected in 2015, appeal pending
		Europe	MDM	2015	Maintained in an amended form; under appeal
		India	DNP+, I-MAK	2013	Under examination
		Russia	ITPCru	2015	Partially revoked (Appeal)
		Thailand	AAF	2016	Under examination
Sofosbuvir (base compound/ molecule)	WO2005003147 "Modified fluorinated nucleoside analogues"	Argentina	FGEP	2017	Opposition filed
		Brazil	ABIA	2015	Opposition filed, preliminary rejection by ANVISA, under examination
		China	I-MAK	2017	Invalidation filed, case pending
		Europe	MDM	2017	Under examination
		Europe	MSF	2017	Under examination
		Europe	Consortium of six European NGOs	2017	Under examination
		India	DNP+, I-MAK	2013	Refused first but granted later. In the process of appeal
Sofosbuvir (polymorphs)	WO2011123645 "Nucleoside phosphorami-dates"	India	DNP+, I-MAK	2017	Under examination
		Ukraine	AUN of PLWH, I-MAK	2015	Under examination
Sofosbuvir (process)	WO2012012465 "Methods for the preparation of diastereomerically pure phosphoramidate prodrugs"	Ukraine	AUN of PLWH	2016	Rejected
Sofosbuvir/ ledipasvir (compound)	WO2013040492 A2 "Methods for treating HCV"	Ukraine	AUN of PLWH	2016	Under examination

Table 4: Sofosbuvir registration and management of intellectual property in Ukraine

Period of registration	Trademark	Active pharmaceutical ingredients	Manufacturer	Intellectual property	Declared wholesale prices*, US$
31.08.2018-31.03.2019	Myhep	sofosbuvir, 400 mg, film-coated tablets	Mylan Laboratories Limited, India	Drug is manufactured under license from Gilead Science Ireland UC	no data available
09.10.2015-09.10.2020	Sovaldi	sofosbuvir, 400 mg, film-coated tablets	Gilead Sciences, Ireland UC	Patent of Ukraine № 110354 Patent of Ukraine № 115664	15550
20.11.2018 20.11.2025	Virpas	ledipasvir, 90 mg, sofosbuvir, 400 mg, film-coated tablets	Strides Shasun Ltd, India	Drug is manufactured under license from Gilead Science	no data available
07.11.2018-07.11.2023	Sofgen	sofosbuvir, 400 mg, film-coated tablets	Hetero Labs Limited., India	Drug is manufactured under license from Gilead Science	120
07.11.2018-07.11.2023	Virso	sofosbuvir, 400 mg, film-coated tablets	Strides Shasun Ltd, India	Drug is manufactured under license from Gilead Science	no data available
07.11.2018-07.11.2023	Sofgen-L	ledipasvir, 90 mg, sofosbuvir, 400 mg, film-coated tablets	Hetero Labs Limited., India	Drug is manufactured under license from Gilead Science	220
29.03.2017-29.03.2022	Harvoni	ledipasvir, 90 mg, sofosbuvir, 400 mg, film-coated tablets	Gilead Sciences, Ireland UC	Patent of Ukraine № 110354 Patent of Ukraine № 115664	17314
31.10.2018-31.10.2023	Epclusa	velpatasvir, 100 mg, sofosbuir, 400 mg, film-coated tablets	Gilead Sciences, Ireland UC.	Patent of Ukraine № 110354 Patent of Ukraine № 115664	no data available

*-according to https://www. apteka. ua/drugsearch?lang=en

Clinical studies carried out in Ukraine have shown that the advantages of the second generation DAAs drugs are the possibility of oral treatment with a reduction in the number of times the drug is taken, a decrease in the duration of HCV treatment (up to 8-24 w) with an improvement in the safety profile and an increase in the effectiveness of therapy 90% [7,69,70]. The economic component, as well as social and political support are critical factors determining the possibility of elimination in terms of identifying the disease, its diagnosis and strategies to combat it.

In order to increase the availability of sofosbuvir for patients with hepatitis C is necessary the use of the "flexible" mechanisms of the TRIPS Agreement (Agreement on trade-related aspects of intellectual property rights), namely involving the grant of compulsory licenses, the implementation of parallel imports, the tightening of the criteria for patentability etc. [71-80].

CONCLUSION

Data from clinical studies abroad and meta-analyses indicate that sofosbuvir is one of the most promising drugs for the treatment of chronic HCV infection. Its indisputable advantages are that this drug can be used with different genotypes of the virus, decompensated liver function, it is well tolerated. Sofosbuvir has an improved safety profile and a low probability of viral resistance. The drug is recommended by the World Health Organization, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD/the Infectious Diseases Society of America (IDSA), and also entered the Unified clinical protocol on primary, secondary, tertiary care "Viral hepatitis C in adults" of Ukraine (2016).

The high cost of sofosbuvir is due to the powerful patent protection. As mechanisms for working with patent barriers, it is recommended to use the flexible mechanisms of the TRIPS Agreement: the grant of compulsory licenses, the implementation of parallel imports, the tightening of the criteria for patentability (prohibition of patenting new forms that do not improve therapeutic efficacy).

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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