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The use of sofosbuvir for the treatment of recurrent hepatitis C after liver transplantation

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The article presents the experience of direct-acting antiviral (DAA) drug treatment for hepatitis C in the patients after liver transplantation. The end-stage liver disease caused by hepatitis C is the main indication for orthotopic liver transplantation (OLT). In 2013, the first agent in the class of antiviral drugs directly acting on hepatitis C virus (HCV) was introduced into clinical practice. That was sofosbuvir, a HCV polymerase inhibitor, that could be used without interferon alpha.

Materials and methods. *The study enrolled 33 liver transplant recipients with recurrent hepatitis C. Thirty-five courses of antiviral therapy (AVT) were conducted with sofosbuvir being one of AVT components.*

Results. *By the time of analysis, 21 patients had completed the antiviral therapy. All the patients showed an initial response to the antiviral therapy, HCV aviremia was achieved. In 3 patients, with the evaluable*

sustained virologic response (SVR), a renewed HCV replication was observed in the first weeks after the AT completion.

Conclusion. *The new direct-acting antiviral drugs offer an effective antiviral therapy to all liver graft recipients with recurrent HCV.*

Keywords: Sofosbuvir, chronic hepatitis C, liver transplantation

The terminal stage of chronic hepatitis C is the leading cause of orthotopic liver transplantation (OLT) in Russia and in the world [1, 2]. The replication of HCV after liver transplantation resumes in all the recipients in whom it was observed prior to OLT, and the disease progression accelerates significantly. The highest risk of the graft loss is seen in patients with fibrosing cholestatic hepatitis (FCH) C, and also in the subgroup of patients with septal fibrosis (METAVIR stage F2 or higher) developing by the end of the first year after the OLT [3]. At 5 years, the graft cirrhosis develops in 20-30% of recipients who have received no antiviral therapy (AVT) [4, 5]. In contrast, a sustained virological response (SVR) to AVT in liver transplant recipients has been associated with improved clinical outcomes, including stabilization and regression of fibrosis [6, 7].

Until recently, the AVT potential in the group of patients under discussion has been limited. Pegylated interferon (pegIFN) alpha-2 formulations in combination with ribavirin allowed the SVR achievement in 13-43% of cases. A considerable number of adverse effects the need in a long-term treatment (for a year) precluded from administering such therapy to all the patients with recurrent hepatitis C [8]. With the advent of HCV protease inhibitors of the 1st generation (telaprevir and boceprevir), the efficacy of the triple AVT has increased to 60%, however, the number of adverse effects has also increased, as well as the number of serious drug

interactions with calcineurin inhibitors that greatly restrict the use of telaprevir and boceprevir in patients after liver transplantation [9-11].

In December 2013, the first agent in the class of antiviral drugs directly acting on hepatitis C virus (HCV) was approved in the USA. That was sofosbuvir, an inhibitor of HCV polymerase that may be used not only in combination with ribavirin and pegIFN, but in interferon-free regimen. The implementation of sofosbuvir, and a number of other direct-acting antiviral (DAA) drugs subsequently has completely changed the existing paradigm of AVT for hepatitis C both in immunocompetent patients, and in patients with recurrent hepatitis C receiving immunosuppressive therapy after OLT. Sofosbuvir is a potent agent against all known HCV genotypes, has a high resistance barrier and a favorable safety profile. Most adverse events observed in clinical trials of sofosbuvir were associated with a simultaneous use of pegIFN and(or) ribavirin [12]. Sofosbuvir shall be taken orally at a dose of 400 mg once daily, irrespective of food intake. The drug has no clinically significant drug interactions with cyclosporine and tacrolimus, the main drugs providing immunosuppression after OLT [13].

Charlton et al. (2015) studied the possibility of using sofosbuvir in combination with ribavirin within 24 weeks in 40 liver transplant recipients with pronounced fibrosis or cirrhosis of the graft. The SVR indicating the virus eradication was achieved in 28 patients (70%), in most of whom the previous course of therapy with pegIFN and ribavirin appeared ineffective. In all the cases of sofosbuvir and ribavirin treatment failure, its cause was the relapse after the therapy course completion, rather than a virologic breakthrough during the therapy or an initial lack of response. In neither case the development of drug resistance to sofosbuvir was observed [14]. Before the authorization of the sofosbuvir and ribavirin combination for the

treatment of chronic hepatitis C in immunocompetent patients, the program of charity access to this drug combination was started for liver transplant recipients with severe recurrent hepatitis C, including FCH and decompensated cirrhosis of the graft. Preliminary results of that program were summarized by Forns et al. (2015). The ribavirin and sofosbuvir combination therapy for 24-48 weeks was given to 104 patients with a life expectancy of less than a year. There was a heavy early relapse of hepatitis C in half of the cases, other 52 patients had the graft cirrhosis diagnosed more than one year after surgery. In 12 cases, the liver retransplantation was performed that made impossible to assess correctly the AVT efficacy. Among the rest 92 patients, the SVR was achieved in 54 (59%). The changes in liver functional test results were assessed in 103 patients demonstrating an improvement in 57.3%, no changes over time in 22.3% of patients, and a deterioration or death in 20.4%. [15].

By the time of sofosbuvir registration for clinical use in patients with chronic hepatitis C, ribavirin and pegIFN had already been used in routine practice in combination with another contemporary DAA: simeprevir, a HCV serine protease inhibitor of the 2nd generation. The researchers have a natural desire to explore the potential of sofosbuvir and simeprevir combination therapy for the treatment of patients with chronic hepatitis C. As sofosbuvir was noted to have a pan-genotype activity, the sofosbuvir and ribavirin combination therapy was used to treat patients with genotype 1 to 4 HCV infection. Simeprevir has an antiviral activity only against genotype 1 HCV infection (and genotype 4 HCV that is extremely rare in Russia), so the simeprevir and sofosbuvir (± ribavirin) combination was investigated primarily in patients with the 1st genotype.

In April 2015, the group of authors in the USA conducted a meta-analysis of 9 original studies that included overall 325 liver transplant recipients who had received the simeprevir and sofosbuvir (± ribavirin) combination therapy [16]. Based on the cumulative data analysis, the SVR rate was 88% (95% CI 83.4-91.5%). The AVT efficacy was not significantly different between the retrospective and prospective studies that seemed to reflect a low incidence of premature AVT discontinuation. In 2 studies that provided the data on liver graft fibrosis, the SVR rate in the patients with genotype 1 HCV infection was 93.6% in those with mild fibrosis (METAVIR Stage F0-F2) and 76.9% in those with severe fibrosis (METAVIR Stage F3-F4). A good tolerability of the drug combination should be emphasized: the most frequent adverse effects include: weakness (21%), skin reactions such as rash, itching, and photosensitivity (15%), headache (9%), and gastrointestinal symptoms (nausea or diarrhea in 6% of cases).

The similarly high rate of SVR (93-96%) in the treatment of recurrent hepatitis C induced by the 1st genotype virus was reported by other authors whose studies were not included in the meta-analysis above [17-19]. Issa et al. (2016) have recently published the results of using sofosbuvir and simeprevir combination in 5 patients with FCH, a highly severe form of post-transplant hepatitis C. HCV aviremiya was achieved in all 5 patients treated by the authors; one of the patients with multiple co-morbidities died of sepsis on the 6th week of therapy. In the rest 4 cases, aviremiya was persistent [20]. The use of the sofosbuvir and simeprevir combination has been limited not only to HCV genotype, but also to the choice of a calcineurin inhibitor for the maintenance immunosuppression. With simultaneous use of simeprevir and cyclosporine, the simeprevir

concentration increases 5 times, and the combined use of these drugs is not recommended because of simeprevir toxicity risk [21].

The next step in the development of the AVT against recurrent hepatitis C after the OLT was to study the potential of pan-genotype therapy with sofosbuvir in combination with daclatasvir, a NS5A replication complex inhibitor. Both drugs have a favourable safety profile, a relatively few number of clinically significant drug interactions, no interactions with cyclosporine and tacrolimus [22, 23].

In phase III study (ALLY-1), sofosbuvir was administered in combination with daclatasvir in standard doses and with ribavirin at an initial dose of 600 mg/day. The treatment duration was 12 weeks for the patients predominantly with genotype 1 HCV infection who had previously received or not received pegIFN and ribavirin. The study included two specific groups of patients: those with decompensated cirrhosis (Child B or C; n = 60), and those who underwent the liver transplantation (n = 53). The SVR12 rate in patients with recurrent hepatitis C after OLT was 94% [24]. There were no serious adverse events related to sofosbuvir and(or) daclatasvir and no clinically significant drug interactions with all combinations of immunosuppressive agents (cyclosporine, tacrolimus, everolimus, sirolimus, corticosteroids, mycophenolate). In 4 cases, the patients with hepatocellular carcinoma underwent OLT while on AVT with sofosbuvir and daclatasvir. Three patients resumed receiving antiviral drugs within 12 weeks after OLT. SVR was achieved in all 4 cases, including the recipient who had received the liver from the donor infected with HCV (genotype 1a).

Fontana et al. (2016) reported the use of AVT with daclatasvir in combination with sofosbuvir and(or) simeprevir in 97 patients with severe

recurrent HCV of the graft, 93% of them had genotype 1 HCV infection [25]. Graft cirrhosis was observed in 31% of the cases, and FCH was in 37%. In that study, daclatasvir being a mandatory component of AVT was administered in combination with sofosbuvir in 77 patients, in combination with simeprevir in 18 patients, and 2 patients received three drugs. Overall, 35% of the patients also took ribavirin, namely 20 patients (26%) receiving the daclatasvir and sofosbuvir combination, and 12 patients (67%) receiving the daclatasvir and simeprevir combination. It is interesting to note that the failures were observed only in the subgroup of patients treated with the daclatasvir and simeprevir combination: a virologic breakthrough during therapy occurred in 3 cases, HCV recurrence after of AVT completion was seen in 2 other cases. Six patients died while on AVT, 2 others died after its completion. In any case, the patient deaths were not related to AVT.

The ledipasvir and sofosbuvir combination with ribavirin was studied in patients with recurrent hepatitis C virus genotype 1 and 4 infection in one of the largest prospective studies SOLAR-1 [26]. That study with broad inclusion criteria enrolled 229 patients with graft fibrosis of various severity, compensated and decompensated cirrhosis, and also FCH.

The patients with compensated cirrhosis received ribavirin in a standard dosage adjusted for the body weight (1000 or 1200 mg); and in those with decompensated cirrhosis, the initial dose of ribavirin was 600 mg/day. The patients were randomized into subgroups to receive the therapy either for 12 weeks or for 24 weeks. One of the most important results of the study was the demonstration of a comparable efficacy between the 12-week and 24-week courses of therapy with sofosbuvir, ledipasvir and ribavirin. SVR ranged between 96-98% among the patients with graft fibrosis and compensated cirrhosis, between 85-88% among the patients with cirrhosis

(Child class B), and between 60-75% among the patients with decompensated cirrhosis (Child class C; n = 9). The treatment also proved efficient in all 6 patients with FCH. The majority of patients with graft cirrhosis showed their MELD score improved or remained unchanged. In general, the authors emphasized a good tolerability of therapy and no clinically significant drug-drug interactions between the antiviral drugs and immunosuppressants. Equally good results were obtained in a similar design SOLAR-2 study [27]. In the patients with genotype 1 HCV infection, the SVR was 96-98.6% in those with a compensated liver graft disease, 91-96% in those with decompensated cirrhosis (Child class B and C) as a result of a 12-week and 24-week AVT. SOLAR-1 and SOLAR-2 studies included a total of 444 liver recipients.

Currently, a new drug combination of sofosbuvir with a HCV NS5A inhibitor velpatasvir is under investigation for use in different groups of patients with hepatitis C, including liver transplant recipients.

Patients and Methods

By the time of writing this paper, we had initiated 35 AVT courses containing sofosbuvir as one of the AVT components to 33 liver recipients with recurrent hepatitis C. Two patients received repeated AVT courses. Three patients received AVT including pegIFN, sofosbuvir, and ribavirin for 12 weeks. Four patients received AVT with the combination of sofosbuvir and ribavirin for 24 weeks (n=3) or for 20 weeks (in one patient the therapy was discontinued due to anemia). Five patients received PVT with the combination of sofosbuvir and simeprevir for 12 weeks. In 17 patients, the AVT was conducted using the combination of sofosbuvir and daclatasvir (among 7 patients who completed therapy, including 5 patients on a 24-week

AVT, and 2 patients on a 12-week AVT course). In 6 cases, the treatment was given in a fixed dosage combination of sofosbuvir and ledipasvir for 12 weeks. Clinical characteristics, and virological characteristics of patients are presented in Tables 1, and 2, respectively.

Table 1. Clinical characteristics of patients with recurrent hepatitis C who received antiviral therapy containing sofosbuvir

AVT regimen	Gender, m/f	Age, years (M; 95% CI)	AT activity < 5 ULN / ≥ 5 ULN	Liver fibrosis (METAVIR) <3/3-4/NA	The initiation month after OLT (M; min.-max.)	Tacrolimus / cyclosporine / everolimus
SOF/PI/R (n = 3)	2/1	52.7 (44, 49, and 65)[1]	2/1	1/2/0	27.5 (6-42)	1/2/0
SOF/R (n = 4)	3/1	51.0 (40.3; 61.7)	2/2	1/2/1	28.7 (7-71)	4/0/0
SOF / SIM (n = 5)	3/2	57.4 (50.3; 64.8)	3/2	1/2/2	28 (5-56)	4/1/1
SOF / DAC (n = 17)	13/4	50.1 (46.4; 53.7)	10/7	8/5/4	25 (2-85)	13/4/4
SOF / LED (n = 6)	4/2	54.7 (48.8; 60.5)	3/3	1/4/1	31.5 (4,8-82)	6/0/1

[1] the age of three patients listed in parentheses.

Note: SOF: sofosbuvir; PI: pegylated interferon; R: ribavirin; SIM: simeprevir; DAC: daclatasvir; LED: ledipasvir; ULN: upper limit of normal; NA: not available; AT: aminotransferase.

Table 2. Virological characteristics of patients with recurrent hepatitis C who received antiviral therapy containing sofosbuvir

AVT regimen	HCV genotype			HCV viremia Log10 IU (95% CI)	Failure of the previous AVT course	
	1b	3	2k / 1b		PI/R	DAA
SOF / PI / R	2	1	-	5.5; 5.8; 7.2[1]	2	2
SOF / R	2	2	-	6.5 (5.1; 6.8)	2	-

SOF / SIM	5	-	-	7.3 (6.3; 8.3)	2	1
SOF / DAC	7	9	1	6.7 (6.1; 7.2)	8	3
SOF / LED	6	-	-	5.7 (3.8; 7.6)	2	1

[1] viremia (log10 IU) in three patients is listed.

Results

By the time of making the analysis, 21 patients had completed the AVT. The SVR assessment (i.e. the follow-up for 12 weeks after the AVT completion) was possible in 18 of them. The AVT results are shown in Table 3.

Table 3. The efficacy of antiviral therapy containing sofosbuvir

AVT regimen	n	Complete biochemical response [1]	Response at AVT completion	SVR	Relapse	Continue treatment / observation
SOF/PI/R	3	2/2	3	3	0	0
SOF/R	4	3/4	4	3	1	0
SOF/SIM	5	2/2	5	3	2	0
SOF/DAC	17	10/12	7	5	0	10/2
SOF/LED	6	2/3	2	1	0	4/1

[1] Normalization of ALT and AST activities from the number of patients with initially increased ALT and AST activities.

All patients had an initial response to AVT, HCV aviremia was achieved. In 3 of 18 patients with evaluable SVR, a resumed HCV replication was noted in the first weeks after the AVT completion. These cases are discussed below. None of the patients had a primary lack of SVR

or a HCV replication "breakthrough" while on AVT. Thus, the SVR rate in our patient population treated with different sofosbuvir-containing regimens was 83%.

In 7 patients, the transaminase activities were within the normal range at the start of AVT. In 4 patients, a complete biochemical response was not achieved, despite HCV aviremia. Probably, the factors that played the role in the genesis of increased ALT and AST activities in these patients differed from the viral ones (steatosis?). In other 5 cases, any judgements on obtaining a complete biochemical response were incorrect because of low duration of therapy. In other patients, the HCV aviremia was accompanied by the normalization of blood serum transaminases.

None of our patients experienced any DAA-related adverse events while on therapy.

Discussion

Since 2014, a revolution has occurred in the field of AVT for HCV. The long-term therapy regimens applying the parenteral administration of pegIFN agents in combination with ribavirin, and (from 2011) with one of HCV protease inhibitors, have been replaced by interferon-free AVT regimens where all the drugs should be taken orally. The efficacy of such regimens has increased to 90% and over, and the tolerability is comparable with the tolerability of placebo. The standard duration of the course has been reduced from 48 weeks to 12 weeks, and some schemes enable us to give up both the interferon and ribavirin.

Currently, three DAA classes are used for the treatment of hepatitis C, which differ in their mechanism of action. They include the virus serine protease inhibitors of the 2nd generation, the polymerase inhibitors, and also

the NS5A complex inhibitors playing an important role in HCV replication. By the time of writing this paper, from 2 to 5 dosage forms and their combinations (fixed-dose and individualized) had been registered in each class of drugs.

An essential characteristic of AVT in the recent 2 years has been a practical quarterly revision of international recommendations for hepatitis C management [28]. PegIFN was rejected from use gradually. Initially, the new DAA drugs were tested in pegIFN- and ribavitin-containing schemes of therapy. That fate did not bypass sofosbuvir either; the drug that demonstrated excellent results when applied in combination with pegIFN and ribavirin for the treatment of patients any HCV genotype infection [29, 30]. Before 2014, there were scarce reports on using sofosbuvir in liver transplant recipients; those were mainly case reports or descriptive case series. Sofosbuvir for the treatment of our first patients was supplied by the manufacturer as part of a charity access program. Accordingly, those were the most serious cases. Two of 3 cases were the patients with graft cirrhosis in whom the preceding AVT courses with pegIFN, ribavirin, and telaprevir proved ineffective. A 12-week therapy with pegIFN, ribavirin, and sofosbuvir led to achieving SVR that lasted for over the next years, and also resulted in a significant clinical improvement. Within 2 years following the AVT completion, the patients with graft cirrhosis displayed no such outcomes as liver cancer, a decompensation, a need to be placed on a waiting list for liver transplantation.

Our next series included 4 patients who received the first registered interferon-free regimen: the combination of sofosbuvir and ribavirin for 20-24 weeks. The efficacy of this therapy can exceed 90% in immunocompetent patients, depending on the previous treatment experience and the presence of

cirrhosis [31], and only 70% in liver transplant recipients, as has been shown lately [14]. Currently, that regimen has ceased to be considered the best and is not recommended any more for the treatment of patients with recurrent hepatitis C [28]. Despite a small number of patients, our experience herewith has been consistent with the literature data. No success was achieved in one of our four recipients with graft cirrhosis who had not previously responded to the triple therapy with pegIFN, ribavirin, and telaprevir. We studied the polymorphisms that determined the drug resistance in that patient. There was no evidence of resistance to any sites of NS3, NS5A, and NS5B. We recently have initiated the third course of AVT comprising sofosbuvir, daclatasvir, and ribavirin. The planned duration of the course is 24 week. A complete response was obtained in 3 patients, including the patient with graft cirrhosis and relapse after the course of pegIFN and ribavirin, and also the female patient with contraindications to pegIFN agents (autoimmune hepatitis).

The treatment results in 5 patients who received a combination of sofosbuvir and simeprevir for 12 weeks appeared worse than we expected. Despite there were no patients with graft cirrhosis in this subgroup, two recipients had a relapse after the treatment completion. In one case, T54S, D168E polymorphisms were identified in NS3 region that conditioned the resistance to protease inhibitors. Current recommendations [28] consider the sofosbuvir and simeprevir combination as one of the options, leaving the ribavirin inclusion in AVT scheme at the discretion of the attending physician. Perhaps its administration could have improved the treatment outcomes in our patients.

In the majority of our patients, the AVT courses being considered the most efficient nowadays were initiated; they comprised the combination of

sofosbuvir and one of the NS5A fragment inhibitors: ledipasvir (n = 6) or daclatasvir (n = 17). The sofosbuvir and ledipasvir combination is a fixed one (both active ingredients are combined in a single dosage formulation). We used it only in the patients with genotype 1 HCV infection, as far the ledipasvir efficacy is not considered high enough in patients with genotype 3 HCV. The combination of sofosbuvir and daclatasvir is pan-genotype; and we used it for the treatment of 7 patients with genotype 1 HCV, 9 patients with genotype 3 HCV, and in 1 patient with a recombinant (2k/1b) genotype HCV. We could preliminary suggest a 100% efficacy of this DAA drug combination in our group of patients, as the HCV aviremia was achieved in all the cases and converted into the SVR in the 6 cases where the follow-up after the AVT completion was of adequate duration to assess the SVR.

The AVT duration and the need to include ribavirin in the AVT scheme are of particular interest among the factors that have been discussed in literature as those influencing on the efficacy of AVT with sofosbuvir and a NS5A inhibitor. Initially it was supposed that the immunosuppression effect will significantly reduce the effect of a standard AVT course. That reflected the requirement to conduct the AVT for 24 weeks, including ribavirin. Of our 7 patients who achieved the SVR (and who, therefore, had started the AVT earlier than others), 4 patients received the AVT for 24 weeks. Later it was demonstrated that the triple AVT comprising ribavirin was sufficient for 12 weeks [14, 27]. The efficacy of a 12 week AVT course with sofosbuvir and daclatasvir combination without ribavirin was shown in the French study CO23 ANRS CUPILT [32]. Of 137 patients enrolled in the study, 21 received the AVT in the above described regimen (including 11 patients with pronounced fibrosis and graft cirrhosis). A persistent response was achieved by all patients. In the study by Fontana et al. (2016)

summarizing the results of using the sofosbuvir and daclatasvir combination in 77 liver transplant recipients in routine practice, there was no differences in the SVR rates between the subgroups of patients receiving and not receiving ribavirin (100% vs. 88%, respectively; p = 0.18). We should emphasize that all the patients who had not achieved SVR died before the follow-up completion, i.e. a correct assessment of the SVR was impossible [25].

The role of pre-existing mutations of resistance to NS5A inhibitors remains poorly understood. In ANRS CUPILT SVR study, the SVR was achieved by 132 of the 134 patients (98.5%) who completed the AVT. A virologic breakthrough was observed in one patient on the 11th week of the AVT; a relapse after the AVT completion was reported in another case. Both patients had an existing mutation of resistance to NS5A Q30R, and a Y93H mutation also emerged in the patient with relapse [32]. Mutations associated with resistance to NS5A identified at codons 28, 30, 31 and 93, were found in 22 of the 112 patients included in the ALLY-1 study [24]. Nevertheless, the SVR was achieved in 18 patients (82%), which was comparable to the SVR rate (90%) in a cohort of patients who had had no such mutations prior to AVT. Meanwhile, in all 13 patients in whom the therapy proved inefficient, the NS5A resistance mutations were identified after recording a relapse or breakthrough. The need for routine determination of drug resistance mutations prior to AVT is not regulated by international recommendations. In our routine practice, we have studied these polymorphisms in the cases of poor experience with DAA-comprising therapy since such an assay became available.

Conclusion

The revolutionary changes occurring in the therapy of chronic hepatitis C in the recent 2 years, have involved such a specific patient population as liver recipients with recurrent hepatitis. Sofosbuvir became the first formulation that enabled to reject using pegINF in the hepatitis C treatment. Its use for 12 weeks in combination with other DAA drugs, especially with HCV NS5A inhibitors, ensures the virus eradication that is close to 100%. The combinations of sofosbuvir and daclatasvir or sofosbuvir and ledipasvir have good safety profiles and can be used concurrently with tacrolimus, everolimus and cyclosporine. The emergence of new DAA drugs makes the AVT therapy possible for almost all liver graft recipients with HCV infection that might result in a significant increase in graft and recipient survival rates.

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