

**The use of telaprevir for the treatment of hepatitis C in patients
undergoing liver transplantation**

(Literature review and clinical experience)

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The article summarizes published data on the therapeutic use of the 1st generation hepatitis C virus (HCV) protease inhibitors (boceprevir and telaprevir) as antiviral therapy in patients undergoing liver transplantation. The efficacy and tolerability of the therapy have been assessed with a special emphasis on the drug interactions between calcineurin inhibitors and HCV protease inhibitors. The article is illustrated with authors' case reports.

Keywords: liver transplantation, telaprevir, antiviral therapy, Hepatitis C virus.

A HCV infection is a major cause of the end-stage liver disease and the main indication for orthotopic liver transplantation (OLT) in Russia and other countries of the world [1]. In all liver transplant recipients who have a detectable HCV RNA in blood at the time of transplantation, the infection reappears in a post-transplant period often leading to a severe graft disease.

One-third of such recipients develop a graft cirrhosis at 5 years after the OLT. A further disease progression results in a decompensation in approximately 40% of cases in the following year. Currently, retransplantation remains the only treatment for decompensated cirrhosis of the liver transplant. From 2% to 8% of liver transplant recipients develop a fibrosing cholestatic hepatitis (FCH), a specific type of hepatitis C, characterized by a particularly high HCV viremia, a rapidly developing portal and intralobular fibrosis, the bile duct proliferation, cholestasis, and ballooning degeneration of hepatocytes with a moderate inflammatory response [2]. Without an efficient antiviral therapy (AVT) these patients have a poor prognosis.

The antiviral therapy with pegylated interferon alpha (PEGIFN) and ribavirin (RIB) had been a standard of care (SOC) for HCV-infected liver transplant recipients up to 2011. A sustained virologic response (SVR) achieved in this patient population allowed the improvement of the graft and recipient survival rates, but the rate of SVR among the patients treated with PEGIFN/RIB did not exceed 30% [3-5]. The advent of direct-acting antiviral (DAA) agents has opened up a new era in the treatment of HCV-related liver diseases. Due to a rapid progression of hepatitis C after OLT, any new options of AVT should be immediately studied in this patient population. To date, a world-wide clinical practice has accumulated some experience in using HCV protease inhibitors (PIs) of the first generation, namely telaprevir and boceprevir, in the most severely ill patients undergoing OLT who are failing to respond to a SOC [6-8]. In December 2012, telaprevir (Insivo®) was registered in Russia as a drug for the treatment of patients with chronic hepatitis C.

Efficacy of a triple therapy with telaprevir or boceprevir

There are only a few studies on the efficacy and safety of telaprevir and boceprevir after OLT. The results of three retrospective studies published in full-text form are summarized in Table.1. Pungpapong et al. (2013) summarized the experience of three centers in which PIs were administered to 60 recipients (25 and 35 patients on boceprevir and telaprevir, respectively) with severe liver fibrosis (\geq F2 by METAVIR) with average follow-up of 35 weeks. Before PI administration, most patients on immunosuppressive therapy were switched from tacrolimus to cyclosporine. At week 4 of PI therapy, the virus ceased to be detectable in 6 patients (17%) who received telaprevir and in 6 other patients (25%) who received boceprevir. At week 12, HCV aviremia was documented in 28 (80%), and 10 patients (40%) in the groups receiving telaprevir and boceprevir, respectively. Four patients being on AVT experienced a virologic breakthrough [6]. Coilly et al. (2013) reported the results of a multicenter study of using PI after OLT. Thirty-seven recipients received a triple therapy with telaprevir (n=19) or boceprevir (n=18). This study included patients with advanced fibrosis (83%), the patients who did not respond to the course of dual therapy (PEGIFN/RIB), and patients with FCH (16%). Aviremia was documented in 19 of 37 patients on triple therapy at week 4, and in 27 patients (76%) at week 12. The SVR rates at week 12 could be assessed in 5 patients who completed the treatment with telaprevir, and in 7 patients who completed the treatment with boceprevir. A SVR was achieved in 6 cases. Six other patients experienced a virologic breakthrough. A complete sequence of NS3 protein fragment was studied in 7 recipients in whom the

treatment appeared ineffective. In each of these cases, the resistance testing showed at least one PI resistance mutation [7].

Table 1. The efficacy of the triple antiviral therapy and the HCV relapse data.

The first author (reference)	Coilly	Pungpapong	Werner
	(7)	(6)	(8)
Patients, n	37	60	9
Medication: BOC/TVR, n/n	18/19	25/35	0/9
A 4-week induction phase, %	70	47	0
Virologic response			
4 weeks,%	56/47	24/17	N/A / 44
8 weeks,%	N/A	40 / N/A	N/A
12 weeks,%	89/58	N/A / 80	N/A / 89
TC,%	72/40	N/A	N/A
SVR12, %	71/20	N/A	N/A

Note: the virologic response was considered positive in case of negative HCV RNA load after 9 courses of triple therapy with or without induction phase; BOC: boceprevir; TC: therapy completed (48 weeks); HCV - hepatitis C virus; N/A: not available; SVR12: a sustained virologic response after 12 weeks of completed antiviral therapy; TVR: telaprevir.

Werner et al. (2012) reported the pilot study results of triple AVT including telaprevir in 9 liver transplant patients. The main component of immunosuppressive therapy was tacrolimus in 4 cases, cyclosporine in 4 other cases, and sirolimus in 1 patient. Seven of 9 recipients completed the 12-week course of triple AVT. Virologic response was achieved in 4

patients at week 4 (in 2 of them the therapy was subsequently interrupted), in 7 patients at week 8, and in 8 patients at week 12 [8].

Interesting are the results of a multicenter North American study CRUSH-C published to date as a summary [9]. The study included 112 liver transplant patients treated with telaprevir (88%) and boceprevir (12%) on a triple AVT. In the majority of patients (96%) the treatment was started with a dual therapy. The induction phase duration was over 60 days in 25% of cases, and over 90 days in 13 %. Virologic response occurred at week 4 in 66% of patients, and at week 12 in 84%. Aviremia HCV maintained from the 4th to the 12th week of triple therapy in 64% of cases. A SVR appeared evaluable in 43 patients at week 4 of follow-up after AVT completion. A sustained response was observed in 65% of cases. The study included 30 recipients with severe liver disease (18 patients with transplant cirrhosis and 12 patients with FCH). Aviremia from week 4 to 12 and SVR were more likely observed in the subgroup of patients with non-severe rather than severe hepatitis (48% vs. 69%, $p=0.05$, and 44% vs. 71%, $p=0.14$ respectively).

Recently published results have demonstrated the possibility of using first-generation PIs to treat those liver transplant recipients who developed a severe hepatitis C of the graft, and in whom the standard PEGIFN/RIB therapy appeared inefficient. The results of a prospective trial of using telaprevir after OLT (REPLACE: NCT01571583) are awaited.

Safety of a triple therapy with telaprevir or boceprevir

AVT safety in patients after OLT is one of its major limitations. Systematic reviews of dual therapy (PEGIFN/RIB) reported the necessity of RIB and/or PEGIFN dose reduction in 70% of patients. The rates of premature discontinuation of therapy make about 30% [3–5]. The major complications of standard AVT include infectious and hemotoxic ones. Table. 2 summarizes the reported in literature adverse events observed in patients on a triple AVT with PIs. The most common complication includes cytopenia (various forms) that may be easily controlled and usually is not life-threatening. More serious complications are the infections that can lead to a decompensated graft disease and even result in a patient's death. Werner et al. (2012) reported a patient in whom the AVT was interrupted on the 2nd week due to a severe pneumonia [8]. Pungpapong et al. (2013) observed 7 cases of infectious complications developed in patients while being on AVT: a periodontal abscess (n=1), a urinary tract infection (2), cellulitis of lower limbs (n=1), sinusitis (n=1), pneumonia (n=1), and herpes zoster (n=1). Two patients died and 3 developed a decompensated graft cirrhosis [6]. In a case series reported by Coilly et al. (2013), the infectious complications occurred in 10 cases, 3 patients died. The authors observed pneumonia (2 cases), urinary tract infections (4 cases), erysipelas, peritonitis, a cytomegalovirus infection, and pneumocystosis with aspergillosis (1 case each) [7]. The triple therapy should not be administered to weak, exhausted patients who had a previous history of decompensated liver disease. An increased risk of acute cellular rejection (ACR) is a specific adverse effect observed in liver transplant recipients on AVT. It occurred in 6% of these patients. The conducted studies found no statistically significant differences in ACR rates

between the groups of patients who had received and had not received AVT [10, 11]. Increased immunosuppression was efficient in most cases of ACR. The risk of biopsy-proved ACR in the patients on a triple therapy made 4-6% that was not increased as compared with the group of patients receiving the dual PEGIFN/RIB therapy [6–8]. In contrast to immunocompetent patients with hepatitis C, the liver transplant recipients did not demonstrate any severe dermatological complications while on therapy with PIs.

Interaction with immunosuppressants

PIs (telaprevir and boceprevir) and the calcineurin inhibitors (cyclosporine and tacrolimus), when used in immunosuppressive therapy after OLT, act as substrates and inhibitors of cytochrome CYP3A4 subunit and p-glycoprotein suggesting possible drug interactions. Narrow range of therapeutic concentrations of immunosuppressants implies a critical nature of these interactions. Plasma concentrations of tacrolimus and cyclosporine increased 70-fold and 4.6-fold, respectively, when co-administered with telaprevir in healthy volunteers. [12]. In case of co-administration with boceprevir, blood levels of calcineurin inhibitors did not increase that much, 17- and 2.7-fold for tacrolimus and cyclosporine, respectively [13]. In contrast, the administration of a single dose of cyclosporine or tacrolimus had no significant effect on the PI pharmacokinetics.

Table 2. Safety data on using the triple therapy for recurrent HCV after liver transplantation.

The first author (reference #)	Coilly (7)	Pungpapong (6)
Patients, n	37	60
Cytopenia		
Anemia (Hb <8 g/dl), %	32	N/A
Leukopenia (NC <1 g/L), %	40	N/A
Thrombocytopenia (PC <50 g/L), %	32	N/A
Management		
RIB dose reduction, %	70	93
Using EPO, %	97	85
Transfusion of packed red blood cells, %	35	53
Using GSF, %	8	33
Using Eltrombopag, %	0	5
Other side effects		
BC ACR, n	0	3
Renal failure, n	5	23
Infections, n	10	7
Death, n	3	2

Note: BC ACR: biopsy-confirmed acute cellular rejection; Hb: hemoglobin; HCV: hepatitis C virus; EPO: erythropoietin; GSF: granulocyte stimulating factor; N/A: not available; NC: neutrophil count; RIB: ribavirin; PC: platelet count; TVR; telaprevir.

Werner et al. (2012) daily measured the trough concentrations of tacrolimus and cyclosporine in 8 liver transplant recipients in the initial 6-8 days of triple AVT [8]. Tacrolimus was administered to patients in a dose of 0.5 mg once a week to maintain a targeted blood levels in the range of 5 to 7

ng/mL. Such weekly dosing of the drug may be consistent with the daily administration of 0.05 mg tacrolimus, i.e. to 22-fold decrease of tacrolimus daily dose from the initial dose level. Blood levels of tacrolimus exceeded 7 ng/mL for 28% time of the treatment duration (with the absolute maximum concentration of 20 ng/mL) and were under 5 ng/mL for 32% time of the treatment duration (the absolute minimum concentration of 2.5 ng/mL).

According to the study protocol, the daily dose of cyclosporine was decreased by 50% from the baseline initially and further on as needed to maintain the blood level in the range of 70-100 ng/mL with daily dosing. The average daily dose of cyclosporine was 48.5 mg that was consistent to an average of 2.5-fold reduction of the baseline dose. The reported cyclosporine concentrations exceeded the targeted ones for 13% time of the treatment duration (the maximum concentration of 206 ng/mL), and were under the targeted ones for 21% time of the treatment duration (the minimum concentration 39 ng/mL). Coilly et al. (2013) reduced the cyclosporine dose by 1.8 times while on treatment with boceprevir and by 3.4 times while on treatment with telaprevir. The tacrolimus dose was decreased by 5.2 times while on therapy with boceprevir, and by 23.8 times while on therapy with telaprevir compared to baseline doses [7].

Thus, the literature data suggest the possibility of using either of the two calcineurin inhibitors in triple AVT, but the practical aspects of their administration have some benefits in favour of using cyclosporin. Besides inconveniences with dosing regime selection in tacrolimus therapy, there is a threat of having its toxic concentrations within 24 hours following the first weekly dosing which may affect kidney function and cause a decreased ribavirin excretion and thus exacerbate the anemia.

We used telaprevir in 3 patients who developed recurrent active rapidly progressing hepatitis C after OLT. Below we report our observations.

Case report # 1

A male patient of 42 years old with body weight of 65 kg, underwent an OLT in November 2011 for a small size hepatocellular carcinoma secondary to a compensated HCV-related liver cirrhosis. After the surgery, the patient received the immunosuppressive therapy with tacrolimus in a daily dose of 2 mg that provided the blood levels of the drug within the range of 7-9 ng/mL. In the early post-transplant period, the patient revealed a recurrent HCV infection (1b genotype) with high viral load (2.8×10^7 IU/mL) followed by the active hepatitis development. As soon as at 4 months following OLT, the ALT activity 12 times exceeded the upper limit of normal (ULN), but a histological examination of the liver tissue detected modest findings: signs of low activity hepatitis with mild fibrosis (A1F1 by METAVIR Scoring System) without a significant rejection (Banff 3). An AVT was initiated with PEGIFN alfa-2a in the standard dose of 180 mg per week and RIB (1000 mg/day). A rapid and marked response in biochemistry was achieved with a decrease in ALT activity to 2xULN, but the level of viremia remained the same; and 24 weeks later, the AVT was discontinued due to its inefficiency, and the patient was regarded as "a non-responder". It is worthwhile to note a good tolerability of the AVT, just a slight hemoglobin decrease, the absence of other adverse events. Soon after the AVT discontinuation, the previous HCV activity resumed, and a year after the AVT had been terminated (in August 2013), the liver biopsy revealed a

severe hepatitis with bridging necrosis; the histological activity and fibrosis were assessed as A4F3.

Due to the inefficiency of the first course of AVT and the rapid progression of the disease, a triple telaprevir-containing AVT was planned that could be started only in late October 2013, almost 2 years after the OLT. The second course of AVT to the patient had to be delayed because of a developed severe pneumonia, hyperglycemia, decompensated liver disease with hypoalbuminemia (30 g/L), and hepatic encephalopathy. During a 2-month patient's stay in the Intensive Care Unit (ICU), a clinical compensation of diabetes and liver function was achieved. Given the drug interactions between telaprevir and calcineurin inhibitors, the patient was switched from tacrolimus to cyclosporine in his immunosuppression therapy. After the cyclosporine dose adjustment, the AVT was started with PEGIFN alpha-2b (80 mg/week), RIB (800 mg/day), and telaprevir at a dose of 2250 mg/day (750 mg, t.i.d.). Before the AVT start, HCV viremia was 3.3×10^8 IU/mL. On the first day of telaprevir administration, the daily dose of cyclosporine was reduced from 150 to 50 mg in a single daily dosing with monitoring the blood cyclosporine trough concentrations every other day. Subsequently, the cyclosporine dose was adjusted to 50 and 25 mg a day to achieve a target drug concentration in the blood. As soon as 2 weeks after AVT had been started, the ALT activity decreased to 2xULN and subsequently (within 8 weeks) returned to nearly normal values (with minimum of 47 IU/L). The HCV RNA load made 200 IU/mL at week 4 on AVT, 620 IU/mL at week 8, and by the 12th week on AVT a virologic breakthrough had been documented with the resumed HCV replication to 1.5×10^6 IU/mL. Thus, despite a significant decrease in ALT and AST

activities, the patient experienced a virologic breakthrough. The AVT was discontinued.

Case report # 2

A female patient, born in 1983, underwent an OLT for decompensated HCV-related liver cirrhosis in February 2009. The postoperative period was complicated by a severe ischemia-reperfusion injury of the graft with ALT and AST activities rising to 10,000 IU/L and 12,000 IU/L, respectively. By the 37th day after OLT the enzyme activities had been nearly normal. As soon as 2 months after OLT, a HCV RNA (1b genotype) resumed with high viral load (5.7×10^7 IU/mL). The patient was on the immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisone. According to the accepted protocol, mycophenolate mofetil and prednisone were subsequently withdrawn at 3 months after the OLT. A needle biopsy of the liver performed on 25.05.2009 revealed a chronic active hepatitis C with a low activity level. With regard to the increase in ALT activity to 3xULN, an AVT was started with PEGIFN alfa-2b in a weekly dose of 50 mg (the patient's body weight being 53 kg), and RIB at a daily dose of 400 mg. By week 4, HCV RNA had slightly decreased to 4.4×10^6 IU/mL. However, while on therapy, the patient experienced an abrupt fall in red blood parameters (min hemoglobin 42 g/L) that coincided with a resumed menorrhagia. The AVT was discontinued at week 6. Transfusions of packed red blood cells were performed, erythropoietin was administered.

After the red blood cell count had returned to normal, in October 2009, a second attempt of AVT with PEGIFN alfa-2b (50 mg per week) for 4 weeks was made without any virologic response. At week 5 the AVT was changed to dual therapy with PEGIFN alfa-2a in a standard dose of 180 mg

per week, and RIB in the dose of 400 mg/day that was further increased to 800 mg/day within a month. Therapy continued for 12 weeks without a virologic response. Erythropoietin and Filgrastim were administered for the developed anemia and neutropenia. AVT was discontinued as considered inefficient (lack of virologic response).

The course of the disease was complicated by the stricture of the biliary anastomosis and the major duodenal papilla. Attempts were made to perform an endoscopic papillosphincterotomy and the biliary drainage. These measures appeared inefficient, and on 20.12.2010 a Roux-en-Y hepaticojejunostomy was performed on an excluded jejunal loop. Subsequently, the patient's follow-up took place predominantly in a local medical facility, her ALT and AST activities intermittently elevated. In December 2011, ALT activity reached 14xULN. A needle biopsy of the liver was performed and the histological examination of a liver tissue specimen verified a monolobular graft cirrhosis of moderate activity (graded as A2 by METAVIR Scoring System). The hepatitis activity spontaneously decreased, and no cirrhosis decompensation developed in subsequent 2 years of follow-up, despite emerged ultrasonographic signs of cirrhosis.

Considering a developed liver graft cirrhosis and a high risk of liver disease decompensation, in November 2013 a decision was taken to make another attempt of the telaprevir-containing AVT. A conversion of immunosuppressive therapy regime from tacrolimus to cyclosporin was undertaken with the cyclosporin daily dose of 150 mg. On November 11, 2013, the therapy was started with PEGIFN alfa-2b at a dose of 80 mg per week, RIB at a dose of 800 mg/day, and telaprevir in the standard dose of 2250 mg/day (split into 3 divided doses). At week 4 of AVT, virologic response was achieved that maintained over subsequent 8 weeks on the triple

therapy and 36 weeks on the standard therapy with PEGIFN alfa-2b and RIB that the patient still received while the article was in press. A specific feature of this AVT course was the development of a moderate depressive syndrome that was controlled by citalopram. From the first day of telaprevir administration, the cyclosporine daily dose was reduced to 50 mg, and subsequently to 25 mg. While on AVT, the patient developed anemia with hemoglobin decrease to 76 g/L by week 12. At week 12 of therapy, the patient experienced a fever with the body temperature elevation to 40°C secondary to the neutrophil count fall to 0.43×10^9 /L. No local foci of infection were identified at X-ray examination. After a single dose of filgrastim and the antibacterial therapy with cefazolin for 3 days, the body temperature returned to normal, and the patient's general condition improved significantly. After completion of telaprevir course, the patient resumed cyclosporine in the dose of 150 mg per day. The treatment with PEGIFN/RIB was continued for the following 36 weeks; the patient received erythropoietin preparations, when necessary. With regard to the developed hypertrichosis, gingival hyperplasia, hypertension, and hyperkalemia while on telaprevir, the immunosuppressive therapy was switched to tacrolimus again. At the moment the article was in press, the patient had had a SVR for 12 weeks of follow-up.

Case report # 3

A female patient, born in 1959, underwent an OLT in October 2011 for a HCV genotype 1b-related decompensated liver cirrhosis. As early as on the 10th postoperative day, a recurrent HCV infection was identified with the viral load of 5.23×10^6 IU/mL. Graft dysfunction signs rapidly emerged and were increasing from the 55th post-OLT day. CMV DNA was identified

in blood. A 4-week therapy with Ganciclovir in a daily dose of 500 mg intravenously (i.v.) was performed with subsequent switch to a valganciclovir therapy in the dose of 900 mg/day. CMV DNA was undetectable in blood; however, despite an ongoing therapy, ALT and AST activities, and blood bilirubin continuously increased, reaching their peak levels in April, 2012, (220 mmol/L for bilirubin, 222 IU/mL for ALT, 54 IU/mL for AST). Needle biopsy of the liver had to be rejected as there were no safe access for the needle due to increasing ascites and a right hydrothorax. The diagnoses of EBV infection, stricture of biliary anastomosis, inadequate immunosuppression were excluded. A recurrent hepatitis C, probably a FCH, were suggested as possible causes of graft dysfunction. AVT was started with PEGIFN alfa-2a in a dose of 180 mcg/week, and RIB in a dose of 800 mg/day (the patient's body weight being 57 kg) with a satisfactory tolerability of the therapy. By the 4th week of AVT, a partial virologic response had been observed with viral load decrease to 4,800 IU/mL, and normal ALT values. But at week 12, a HCV RNA load increased again to baseline values. With regard to an evident clinical improvement, the jaundice resolution, and normal results of all functional liver tests, the AVT was extended to 24 weeks, but without any positive changes in viral parameters: HCV RNA retained in the range between 3.4×10^6 - 6.1×10^6 IU/mL. Within a year following the AVT discontinuation, the patient resumed the signs of active hepatitis. At 23 months after OLT, fibroelastometry showed the hepatic tissue density of 48 kPa, and the biopsy showed the pattern of a developed active cirrhosis of the graft. It should be noted that starting from the first year of AVT and throughout the whole observation period, the patient was predisposed to hypoalbuminemia (albumin levels ranged between 30-35 g/L). A definite

decision to repeat an advisable AVT course with telaprevir was taken soon after the laboratory signs of active hepatitis had resumed in spring of 2013. However, telaprevir became available for the patient only in April 2014.

Routine monitoring of laboratory parameters demonstrated that since August 2013 blood albumin had been below 30 g/L; thrombocytopenia was growing (to 45,000/mcl). After surgery, the patient was on the immunosuppressive therapy with tacrolimus in a daily dose of 4 mg providing the trough blood concentrations of the drug in the range of 7-9 ng/mL. In November 2013 in terms of the preparation for a triple therapy, the immunosuppression was switched to cyclosporine, eltrombopag was started in a dose of 25 mg every other day. The blood bilirubin level was gradually increasing and had reached 73 mcmol/L by March 2014. Renal function test results were within the normal range. There were no ascites. Considering the emerged signs of a graft cirrhosis decompensation (scored 9 by Child-Pugh, 15 by MELD), a decision was taken to start the AVT with an induction phase of PEGIFN alfa-2a in a dose 180 mcg and RIB (600 mg/day). While on therapy, a rapid decrease in ALT to normal values was observed, and AST decreased from 153 to 62 IU/mL. However, bilirubin continued to rise slightly, reaching the peak of 110 mcmol/L. Platelet count could be maintained in the range of 80,000-100,000/mcl. Erythropoietin and filgrastim were administered for the developed anemia (Hb decreased from 119 to 100 g/L), and neutropenia (0.7 cells/mm). Telaprevir became available in April 2014 and was added to the AVT on its 6th week in a standard daily dose of 2250 mg split into 2 divided doses. A rapid virologic response was achieved at week 2 of telaprevir administration and sustained throughout the whole period of telaprevir therapy and after its completion. However, the occurrences of ascites, low limb edema, right-sided

hydrothorax were noted in the patient at week 5 of the triple AVT. Blood albumin was 24 g/L. The albumin infusion, and a diuretic therapy helped to control edema and ascitis, and spironolacton was withdrawn after 5 weeks. Bilirubin and albumin returned to baseline values, ascites did not resume.

A triple therapy tolerability was satisfactory. Thrombocytopenia at the initial stage of AVT was controlled by eltrombopag administration, 25 mg every other day. While on AVT, a gradual decrease of platelet count to 42,000/mcl by week 13 of AVT had been noted that required an eltrombopag dose increase up to 25 mg per day, and up to 50 mg per day at week 14 with a PEGIFN dose reduction to 135 mg per week. The patient experienced hyperthermia twice: at AVT weeks 7, and 11 due to neutropenia. Cefazolin therapy was a success. At week 9 of the triple therapy, the patient developed a Grade 1 skin rash and itching that was treated with desloratadine, 5 mg per day. However, telaprevir had to be discontinued at 3 days before the completion of the triple therapy course because of nasal bleeding, and increased pruritus; the therapy with PEGIFN and RIB was continued. After telaprevir discontinuation, the patient resumed cyclosporine in the dose of 150 mg per day. While this paper was in press, the patient completed the AVT course; she had end-of-treatment response, normal ALT and AST activity levels, hyperbilirubinemia and hypoalbuminemia without aggravation.

Discussion of case reports

Thus, we initiated a telaprevir-containing AVT, to 3 liver transplant recipients who developed a severe form of the liver disease with the risk of the graft loss after OLT. The first case was the patient with a high hepatitis activity and septal fibrosis; the second patient had a compensated graft

cirrhosis. In our third patient, the AVT was started at the stage of decompensated graft cirrhosis and represented a known risk, but alternative therapies were unavailable. Despite different clinical patterns, the patients had some features in common: first, a rapidly progressing course of hepatitis with the development of a severe fibrosis in the first year after the OLT; second, unfavourable for the treatment polymorphisms near the interleukin IL28B locus rs8099917 TG/GG and rs12979860 CT/TT) and as a result, a lack of response to a standard therapy with PEGIFN/RIB. Furthermore, all our patients received the immunosuppressive therapy with tacrolimus that was replaced by cyclosporine prior to initiating the treatment with telaprevir. We chose a target range with the trough cyclosporine concentration of 100-150 ng/mL. A reduction of the cyclosporine daily dose by 3-4 times from the baseline in the patients receiving telaprevir ensured an adequate level of immunosuppression; neither graft rejection episodes, nor cyclosporine toxicity cases were observed.

The efficacy of therapy varied between the patients. In the first case, we were unable to achieve the goal that had been setup. Hepatitis was progressing with the graft cirrhosis development. In the second patient with a compensated cirrhosis, aviremia was achieved, and therefore the chances of a complete success, i.e. virus eradication, remained high. In the third case, the appropriateness of AVT was the most controversial. Unfortunately, the disease progression rate ran ahead of the patient's getting access to telaprevir, and the treatment was initiated only by the time of decompensated liver graft cirrhosis. While on therapy, the liver function did not worsened as assessed by Child-Pugh Score and MELD. We hope HCV RNA will sustain undetectable after the AVT completion and may slow down the disease progression and improve the prognosis. The therapy at this stage can be

regarded as fully justified, if the possibility of liver retransplantation is considered as a prospect.

The first experience of using telaprevir in Russia in the patients undergoing OLT demonstrated a relative safety of this treatment. The CUPIC trial that included immunocompetent patients with cirrhosis demonstrated that the incidence of serious complications on triple therapy with telaprevir or boceprevir and the need in AVT discontinuation depended on the platelet count and blood albumin. The severe complications or even death of the patients with thrombocytopenia ($<100,000/\text{mcl}$) and hypoalbuminemia ($<35 \text{ g/L}$) were observed in 44% of cases [14]. Furthermore, Dultz et al. (2013) showed that the probability of liver cirrhosis decompensation, while on AVT, correlated to MELD score. Thus, the MELD score exceeding 14 is associated with the cirrhosis decompensation probability over 80% [15]. Our third patient's condition was compromised with the need in immunosuppressive drugs (besides her liver cirrhosis), but the treatment course was without serious adverse events; red blood cell transfusions were not required.

Conclusions

The first generation PIs (telaprevir and boceprevir) were the first drugs approved for clinical use in some countries, and in Russia for patients with chronic hepatitis C. The advent of these drugs allowed a double increase in SVR rates among liver transplant recipients with HCV genotype 1 infection. The "clinical life" of telaprevir and boceprevir appeared rather short. Their active use in the United States, Canada, and EU was limited to 2011-2013 that was associated with a number of difficulties in using these drugs. Recently, several DAA agents belonging to the classes of the second-

generation PIs (simeprevir), polymerase inhibitors (Sofosbuvir), and NS5A inhibitors of hepatitis C virus complex (daklatasvir, ledipasvir) have been approved for clinical use in USA, EU, and Canada. Some new molecules and their combinations have entered the completing stage of Phase II clinical trials. New agents demonstrate a comparable clinical efficacy, better safety profile, and fewer drug interactions. Experience of using these drugs after OLT has been limited to case reports or small case series. Among DAA agents, besides boceprevir and telaprevir, only simeprevir have been approved for clinical use in Russia, but its high cost significantly limits the access to treatment. The experience gained in using the first generation PIs after OLT will undoubtedly prove helpful for using new drugs to treat liver transplant recipients for a recurrent hepatitis C.

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