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ORIGINAL ARTICLE

Telaprevir-Based Triple Therapy in Liver Transplant Patients With Hepatitis C Virus: A 12-Week Pilot Study Providing Safety and Efficacy Data

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After liver transplantation (LT), the management of recurrent hepatitis C virus (HCV) infections still remains a major challenge. In HCV genotype 1 patients not undergoing transplantation, the introduction of protease inhibitor (PI)–based regimens has increased the sustained virological response rate significantly. This pilot study investigated both the safety and efficacy of telaprevir (TVR)-based triple therapy in HCV-infected LT patients with a special emphasis on drug-drug interactions between immunosuppressants and PIs. Safety and efficacy data were gathered for 12 weeks for 9 HCV-infected LT patients who were treated with a combination of TVR, pegylated interferon, and ribavirin (RBV) in parallel with immunosuppressive drugs such as tacrolimus (TAC; n = 4), cyclosporine A (CSA; n = 4), and sirolimus (SIR; n = 1). Seven of the transplant patients completed the 12 weeks of triple therapy. At week 4, 4 of the patients were found to be HCV RNA–negative, and importantly, 8 were found to be negative at week 12. During the 12-week course of triple therapy, short-term measurements of immunosuppressant trough levels required individual dose reductions in all patients (CSA, 2.5-fold; SIR, 7-fold; and TAC, 22-fold). Furthermore, two-thirds of the patients exhibited hematological side effects requiring RBV dose reductions, the administration of erythropoietin, or even blood transfusions. In conclusion, this pilot study provides evidence showing that TVR-based triple therapy is effective within the first 4 to 12 weeks in LT patients suffering from HCV genotype 1 recurrence, and it also provides evidence showing that drug-drug interactions between TVR and immunosuppressants can be handled appropriately through the close monitoring of trough levels and adequate dosage adjustments. ***Liver Transpl 18:1464–1470, 2012.*** © **2012 AASLD.**

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In 2011, the first direct-acting antiviral drugs for the treatment of hepatitis C virus (HCV) genotype 1, telaprevir (TVR) and boceprevir, were approved.[1–8] Because of the limited efficacy of pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy,[9,10] HCV is still one of the major reasons for liver transplantation (LT) in the Western world.[11–13] Additionally, the post-LT recurrence of HCV infections is one of the major causes of morbidity and allograft loss after LT.[11,14–16] Because the outcomes of post-LT therapy with the classic antiviral agents PEG-IFN and RBV are at most moderate with respect to a sustained

Abbreviations: CSA, cyclosporine A; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; IFN, interferon; LLOD, lower level of detection; LLOQ, lower level of quantification; LT, liver transplantation; MMF, mycophenolate mofetil; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SIR, sirolimus; SVR, sustained virological response; TAC, tacrolimus; TVR, telaprevir.

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TABLE 1. Characteristics of the Study Cohort Exhibiting the Recurrence of HCV Genotype 1 After LT

Study cohort characteristics	
Age (years)*	60.9 ± 6.7 (51–71)
Sex: female/male (n/n)	2/7
Body mass index (kg/m^2)*	27.1 ± 4.7 (20.4–34.7)
LT and immunosuppression regimens	
Indication for LT: liver cirrhosis/concomitant hepatocellular carcinoma (n/n)	9/7
Immunosuppression	
TAC/CSA/SIR (n/n/n)	4/4/1
MMF as co-medication (n)	3
Steroid as co-medication (n)	5
Time from LT to triple therapy (months)*	52 ± 45.8 (2–168)
Liver histology available after LT (n)	9
Ishak fibrosis score†	2 (0–5)
Time from histology to triple therapy (months)*	24 ± 28.6 (1–96)
Baseline clinical chemistry	
Total bilirubin (mg/dL)*	1.4 ± 1.3 (0.5–4.6)
Alanine aminotransferase (IU/mL)*	60 ± 31 (35–115)
Creatinine (mg/dL)*	1 ± 0.2 (0.7–1.4)
International normalized ratio*	1 ± 0.1 (0.9–1.3)
Hemoglobin (g/dL)*	12.9 ± 1.4 (9.8–14.4)
Leukocytes (/μL)*	4912 ± 1713 (2280–7430)
Platelets (/μL)*	140,000 ± 66,000 (40,000–261,000)
Baseline viral characteristics	
HCV genotype: 1 a/1 b (n/n)	2/7
Pre-LT antiviral therapy: naive/experienced (n/n)	2/7
Post-LT antiviral therapy: naive/experienced (n/n)	1/8
Baseline HCV viral load ($\log_{10}$ IU/mL)*	6.64 ± 0.95 (3.97–7.25)
PEG-IFNα: 2 a/2 b (n/n)	8/1
Baseline RBV dose (mg/kg of body weight)*	11.3 ± 3.4 (6–15.6)
TVR (n)	9

*The data are presented as means and standard deviations (with ranges in parentheses).
†The data are presented as medians and ranges.

virological response (SVR), LT patients constitute one of the classic difficult-to-treat groups.[16–22] Newly introduced protease inhibitor (PI)–based triple therapy now offers promising perspectives for the management of LT patients, although TVR is not yet approved for use in LT patients. A major therapeutic problem is the danger of increased toxicity due to drug-drug interactions between PIs and concurrently used immunosuppressive drugs. PIs such as boceprevir and TVR can significantly modify the levels of immunosuppressive drugs, which are primarily metabolized by the cytochrome P450 3A4 pathway in the liver and, to a lesser extent, in the gut.[23–25]

In this retrospective analysis, we investigated the feasibility of TVR-based triple therapy for LT patients with HCV genotype 1 with respect to (1) efficacy, (2) drug-drug interactions (especially with immunosuppressants), and (3) other safety concerns in LT patients (eg, hematological side effects). We chose to combine TVR with PEG-IFN and RBV in the post-LT setting because of its well-defined 12-week treatment course; this means a shorter time at risk in comparison with boceprevir, which requires a maximum exposure time as long as 44 weeks.

PATIENTS AND METHODS

The clinical features of our study cohort are presented in Tables 1 and 2. In all, 9 patients who were being consecutively treated for the recurrence of HCV genotype 1 after LT were included in this analysis. The mean age of the patients was 60.9 years, and most patients were male (7 patients). All of the patients had cirrhotic livers at the time of LT, and 7 suffered from hepatocellular carcinoma. The average interval between LT and the start of triple therapy was 52 months. All patients underwent liver biopsy at least once after LT, and the median Ishak fibrosis score was 2 (the maximum possible score was 6). Liver function after LT was compensated, except for 1 patient who suffered from a cholestatic recurrence of HCV with a bilirubin level of 4.6 mg/dL at the start of triple therapy (upper normal level = 1.1 mg/dL). The immunosuppressive regimens were heterogeneous: 4 patients received tacrolimus (TAC), 4 patients received cyclosporine A (CSA), and 1 patient received sirolimus (SIR) as the main immunosuppressive agent. Three patients received mycophenolate mofetil (MMF) as a co-medication. Five patients received low-dose steroids (2.5–5 mg/day).

TABLE 2. Individual Characteristics of the 9 Patients in This Analysis

	Patients								
	1	2	3	4	5	6	7	8	9
Selected individual characteristics									
Sex	Male	Male	Male	Male	Female	Female	Male	Male	Male
Age (years)	58	67	71	51	70	59	53	58	61
Weight (kg)	92	97	64	80	70	55	80	66	99
Body mass index (kg/m^2)	32.6	29.9	25.0	24.7	26.7	20.4	27.0	22.8	34.7
Leukocytes at baseline (/μL)	3050	6170	4630	6970	3870	7430	3550	2280	6260
Creatinine at baseline (mg/dL)	1.0	1.2	1.1	1.2	0.7	0.7	1.0	0.8	1.4
Glomerular filtration rate (mL/minute)*	62.2	60.4	66.2	63.8	83.0	85.9	78.5	56.9	51.7
Immunosuppression	TAC	TAC, MMF	TAC	TAC, steroids	SIR, steroids	CSA, steroids, MMF	CSA, steroids, MMF	CSA, steroids	CSA
Cholestatic hepatitis	No	No	No	No	No	No	No	Yes	No
Posttransplant Ishak fibrosis score[†]	5	2	3	2	1	3	2	0	2
Interleukin-28B genotype	CT	CT	CT	CT	CT	TT	CT	CT	CT
HCV treatment history									
Pretransplant treatment/response	IFN, RBV/ nonresponse (then low-dose PEG-IFN)	IFN, RBV, amantadine/ nonresponse (then low-dose PEG-IFN)	—	PEG-IFN, RBV/ nonresponse	PEG-IFN, RBV/relapse	PEG-IFN, RBV/ nonresponse	—	IFN, RBV/ nonresponse	PEG-IFN, RBV[‡]
Posttransplant treatment/response	PEG-IFN, RBV/ nonresponse (then low-dose PEG-IFN)	—	PEG-IFN/ nonresponse	PEG-IFN, RBV/ nonresponse	PEG-IFN, RBV/relapse	PEG-IFN, RBV/ nonresponse	PEG-IFN, RBV/ nonresponse twice (then low-dose PEG-IFN)	PEG-IFN, RBV/ nonresponse (then add-on TVR)	PEG-IFN, RBV/ breakthrough
Current antiviral treatment and dose reductions									
PEG-IFNα dose (μg)*	80 (2 b)	180 (2 a)	180 (2 a)	180 (2 a)	180 (2 a)	180 (2 a)	180 (2 a)	180 (2 a)	180 (2 a)
RBV dose at baseline (mg/day)	800	600	1000	1000[§]	1000	600	1000	1000	600
RBV dose at week 4 (mg/day)	800	400	1000[‖]	—	1000	600	1000	1000	600
RBV dose at week 8 (mg/day)	800	400	—	—	1000	200	1000	1000	400
RBV dose at week 12 (mg/day)	800	200 week 8 to 10 no RBV from week 10 to 12	—	—	1000	200	800	800	400
Erythropoietin use	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
Blood transfusions (U)	2	4	—	—	—	8	2	2	6
Granulocyte colony-stimulating factor use	Yes	No	No	No	No	No	No	Yes	No
HCV response to treatment									
HCV viral load at baseline (IU/mL)	9390	341,000	3,780,000	9,300,000	3,800,000	17,900,000	783,000	339,000	283,000
HCV viral load at week 4 (IU/mL)	Negative	Negative	Negative	<LLOQ, >LLOD[¶]	16	367	<LLOQ, >LLOD	Negative	<LLOQ, >LLOD
HCV viral load at week 12 (IU/mL)	Negative	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative

*Calculated with the Modification of Diet in Renal Disease formula.
[†]The maximum possible score was 6.
[‡]Discontinued because of subjective side effects.
[§]Discontinued at week 2 because of pneumonia.
[‖]Discontinued at week 4 because of subjective side effects of the therapy.
[¶]At discontinuation.
*In parentheses: subtype of PEG-IFN.

Seven patients with HCV genotype 1 b and 2 patients with HCV genotype 1 a were included in our study. As for the interleukin-28B gene polymorphism, 8 of the 9 patients had the CT genotype, which allowed an intermediate response to interferon (IFN), and 1 patient exhibited the unfavorable TT genotype (see Table 2 for details). Seven study patients underwent antiviral treatment at least once before LT, and 8 patients underwent antiviral treatment at least once after LT; obviously, all treatment attempts were concluded without success.

Two patients were on low-dose PEG-IFN at the beginning of triple therapy. These 2 patients exhibited a viral nonresponse to a dual treatment regimen before triple therapy; because of a biochemical response, the treatment regimen was switched to low-dose PEG-IFN monotherapy (patients 1 and 7; Table 2). Another patient had suffered from a cholestatic recurrence of an HCV infection with a peak bilirubin level of 23.5 mg/dL just shortly after LT (patient 8; Table 2). Therefore, patient 8 was treated with dual therapy initially; because he exhibited a viral nonresponse with a rising HCV viral load during therapy, TVR was added after 1 month of dual therapy.

For optimal surveillance as well as the adjustment of immunosuppression trough levels at the beginning of TVR-based triple therapy, the patients were hospitalized during the first 6 to 8 days for the initiation of the triple therapy. Because the dosing of immunosuppressants with TVR-based triple therapy is unclear so far, the trough levels of TAC, CSA, and SIR were measured on a daily basis throughout the time of hospitalization. To prevent any overdosing, TAC and SIR were individually administered in a single dose of only 0.5 mg if trough levels were found to be below the lower limit of the target ranges (TAC, 5–7 ng/mL; SIR, 4–6 ng/mL). Because the drug-drug interaction of TVR with CSA is known to be less pronounced,[26] CSA was administered daily from day 1 onward at a reduced dosage (50% of the original dosage). PEG-IFN was administered in standard doses except to patient 1 (Table 2), who had pronounced thrombocytopenia (40,000 platelets/μl), and therefore continued to receive only low-dose PEG-IFNα2 b. RBV was generally dosed according to the body weight, but prior anemic responses to RBV were taken into account. Therefore, the baseline doses were lower in distinct patients. Because the renal function was acceptable in almost all the patients, it did not have an impact on RBV dosing in the majority of our patients; patient 9 was the exception and received a reduced RBV dose at the baseline (Table 2).

After the initial phase of triple therapy, further surveillance was organized in collaboration with general practitioners and the outpatient department of our hospital. General practitioners were asked to measure and report the trough levels of the immunosuppressants twice weekly. Then, in consultation with our study center, dosages were adjusted to hit the aforementioned target ranges. Visits to the outpatient department were scheduled for treatment weeks 4, 8, and 12 and on demand. During the 12 weeks of triple therapy, clinical chemistry values and HCV viral loads [Roche Cobas AmpliPrep/Roche Cobas TaqMan, Roche Diagnostics GmbH, Mannheim, Germany; lower level of quantification (LLOQ) = 15 IU/mL] were measured at weeks 0, 4, 8, and 12 and individually between these dates. Clinical examinations were performed on the same dates and, if needed, between them.

RESULTS

Efficacy

The mean time on treatment at the end of the observation period was 13 weeks (range = 2–24 weeks). Seven of the 9 patients completed the 12-week phase of TVR-based triple therapy, and they were all still receiving dual therapy with PEG-IFN and RBV at the end of the observation period. In the intention-to-treat analysis, we found that 4 of the 9 patients were HCV RNA–negative at week 4, 7 were negative at week 8, and 8 were negative at week 12. Three of the 5 patients who were not HCV RNA–negative at week 4 had viral loads just around the LLOQ (see Table 2 for details).

In 2 instances, the therapeutic regimen had to be discontinued. One patient suffered from bacterial pneumonia at week 2 and exhibited a viral load below the LLOQ at the time of discontinuation (patient 4; Table 2). The other patient refused any further therapy because of side effects at week 4 (patient 3; Table 2). The latter was HCV RNA–negative at the time of discontinuation and surprisingly remained HCV RNA–negative until the end of the actual observation period (follow-up after discontinuation = 13 weeks).

Immunosuppression Levels With TVR-Based Triple Therapy

Because both TVR and immunosuppressants (eg, calcineurin inhibitors) are substrates of cytochrome P450 3A4 and this can result in significant drug-drug interactions, the dosages of the immunosuppressants had to be modified during concomitant medication. In order to stay within the immunosuppressant target ranges (see the gray bars in Fig. 1), the dosages of the immunosuppressants were reduced during the course of TVR-based triple therapy in a regimen-specific manner: both TAC (n = 4) and SIR (n = 1) had to be given as a single dose per week. These single weekly doses corresponded to calculated average daily dosages of 0.05 mg for TAC and 0.07 mg for SIR, which resulted in dose reduction factors of 22 for TAC and 7 for SIR (Table 3). In contrast, CSA (n = 4) still had to be given daily. The calculated average daily dose was 48.5 mg, which corresponded to a dose reduction factor of only 2.5. During TVR treatment, the trough levels of TAC were higher than the target range of 5 to 7 ng/mL for 28% of the exposure time (absolute maximum level = 20 ng/mL) and were lower than the target range for 32% of the exposure time (absolute minimum level = 2.5 ng/mL; Fig. 1A). The SIR trough levels were higher than the target range of 4 to 6 ng/

mL for 45% of the exposure time (absolute maximum level = 9.3 ng/mL) and were lower than the target range for 54% of the exposure time (absolute minimum level = 2.5 ng/mL; Fig. 1B). The CSA trough levels were higher than the target range of 70 to 100 ng/mL for 13% of the exposure time (absolute maximum level = 206 ng/mL) and were lower than the target range for 21% of the exposure time (absolute minimum level = 39 ng/mL; Fig. 1C).

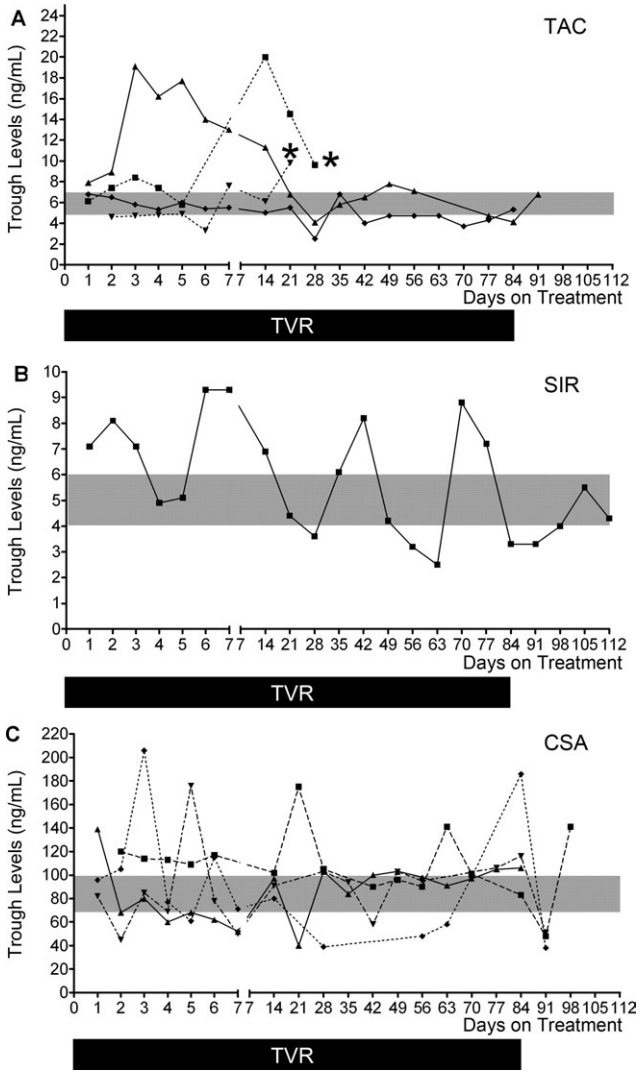

Figure 1. Individual courses of immunosuppressant trough levels during therapy: (A) TAC (n = 4), (B) SIR (n = 1), and (C) CSA (n = 4). The initial in-hospital phase of the triple therapy is represented by the first 7 days. Gray bars indicate the target ranges for trough levels (5–7 ng/mL for TAC, 4–6 ng/mL for SIR, and 70–100 ng/mL for CSA). Asterisks indicate the trough levels of patients who had to discontinue treatment.

Side Effects

Although different manifestations of adverse reactions occurred in most of the patients, no patients were lost during the combined therapy, and treatment had to be stopped because of severe side effects in only 1 case. Four patients were hospitalized during the observation period because of adverse events. One of those patients was hospitalized twice for different reasons. The reasons for in-hospital treatment were bacterial pneumonia, TAC overdosing with renal failure, infectious enteritis with *Yersinia pseudotuberculosis*, exacerbated diabetes mellitus, and raised liver enzyme levels due to histologically proven nonalcoholic steatohepatitis. Notably, the patient with bacterial pneumonia, who had to discontinue treatment, exhibited values within normal ranges at the baseline for white blood cells, platelets, and hemoglobin (patient 4; Table 2). The patient with renal failure due to TAC overdosing had mistakenly taken TAC according to his old pre–triple therapy treatment plan. Six of the 9 patients had anemia with a hemoglobin level lower than 10 g/dL, and 4 of the 9 patients had anemia with a hemoglobin level lower than 8 g/dL. Six of the 9 patients were treated with erythropoietin, and the same number of patients needed blood transfusions (see Table 2 for details). Five of the 9 patients required RBV dose reductions because of anemia. Six of the 9 patients had leukocyte levels lower than 2500/μL, and 3 of the 9 patients had leukocyte counts lower than 1500/μL during therapy. Two of the 9 patients needed granulocyte colony-stimulating factor at least once. Four of the 9 patients had platelet counts less than 50,000/μL with no apparent clinical side effects. Three of the 9 patients had cutaneous adverse reactions, but no patient had a grade 3 or higher rash. The clinical impact of these cutaneous adverse reactions was mild, so the treatment could be limited to the use of moisturizing lotions only. Three patients had increases in serum creatinine levels exceeding 1.5 mg/dL. Two patients had diabetes

TABLE 3. Changes in Immunosuppression During the First 12 Weeks of TVR-Based Triple Therapy

Immunosuppression	Patients (n)	Daily Dose at the Baseline (mg)*	Daily Dose During Triple Therapy (mg)*	Average Daily Dose Reduction Factor†
TAC	4	1.125 ± 0.54 (0.5–2)	0.05 ± 0.04 (0–0.1)	22 (5–33.6)
SIR	1	0.5	0.07	7
CSA	4	122.5 ± 33.4 (80–160)	48.5 ± 19 (26–78)	2.5 (2–3.8)

NOTE: Two patients in the TAC group discontinued treatment at weeks 2 and 4.
*The data are presented as means and standard deviations (with ranges in parentheses).
†Ranges are shown in parentheses.

mellitus: one as a de novo manifestation and the other as an exacerbation of so far nutritionally controlled diabetes. The second patient developed significantly elevated liver enzyme levels. A histological examination showed nonalcoholic steatohepatitis but no signs of acute or chronic allograft rejection.

DISCUSSION

In this retrospective study analyzing the effects of TVR on a small group of LT patients suffering from HCV recurrence, a remarkable number of patients (8/9) had an undetectable viral load at week 12. These data are comparable to those obtained from pretreated patients not undergoing LT,[6,27] and they are also in line with data from another post-LT experience.[28] There is also evidence showing that drug-drug interactions between the PI TVR and immunosuppressants can be controlled if the dosing of the drugs is carefully adapted. The advantage of this triple therapy becomes even more obvious when we compare our findings to data obtained previously from post-LT patients treated with the classic dual regimen of PEG-IFN and RBV.[22] According to our analysis, the direct translation of the typical virological response to PI-based triple therapy (rapid decreases in viral loads in the first 4–8 weeks) into a post-LT setting could promise SVR results similar to those achieved in non-LT patients before.[4,6] Our interim efficacy data are in line with those from the REALIZE trial of TVR-based triple therapy in previously treated (non-LT) patients with null responders, partial responders, and relapsers.[6] In that study, HCV RNA was undetectable at week 4 in 26% to 70% of the patients in different subgroups, and 47% to 93% of the patients were HCV RNA–negative at week 8 (week 12 data were not published). Another study of TVR in previously treated (non-LT) patients, the Protease Inhibition for Viral Evaluation 3 (PROVE3) trial,[29] showed that 47% to 61% of the patients were HCV-negative at week 4, and 53% to 75% were negative at week 12; these data are close to the results of our analysis. Finally, in an interim analysis presented at the 2012 annual meeting of the European Association for the Study of the Liver (EASL), Coilly et al.,[28] who first treated post-LT patients with either boceprevir-based triple therapy (n = 9) or TVR-based triple therapy (n = 1), achieved similar results, although the viral response was slower in comparison with our cohort, probably because of the different antiviral kinetics of the PI boceprevir,[7,8] which was mostly used in their study: 43% of the patients were HCV-negative at week 12, and 57% of the patients were negative at week 24. The antiviral potency of TVR-based triple therapy in the post-LT setting was demonstrated in an impressive way: 1 of our patients quit therapy after just 4 weeks and remarkably remained HCV RNA–negative afterward (follow-up after discontinuation = 13 weeks).

Another goal of this analysis was to assess the feasibility of the co-medication of TVR with cytochrome P450 3A4–metabolized immunosuppressants. Because the magnitude of the drug-drug interactions can vary greatly, the maintenance of stable trough levels of immunosuppressants during the TVR exposure time still remains a challenging problem, especially for TAC and SIR. Thus, the dose reduction factors for the immunosuppressants differed and ranged from 22-fold (for TAC) to 2.5-fold (for CSA). However, except for 1 hospitalization event due to overdosing and renal failure, deviations from the defined target trough levels had no clinical effect, and there were no signs of acute or chronic graft rejection. At the 2012 EASL annual meeting, Coilly et al.[28] reported dose reductions in 100% of the patients receiving TAC and in just 50% of the patients receiving CSA, but no reduction factors were indicated.

Because there is a long-lasting discussion concerning the best immunosuppressant for HCV-positive LT recipients, which has come to a draw for TAC and CSA,[16,30,31] our data, along with the results of Garg et al.[25] and Coilly et al.,[28] could tip the scales in favor of CSA: because of the limited controllability of TAC and SIR concentrations (due to the significantly extended half-lives of these agents), we suggest CSA as the main immunosuppressive agent to be used in the context of future TVR-based triple therapies. Notably, it will be of great interest to correlate SVR data obtained in the future with the respective immunosuppressant regimens applied in these patients.

The major side effect of triple therapy in LT patients is hematological toxicity: two-thirds of our patients developed substantial anemia and, therefore, needed RBV dose reductions, the substitution of red blood cells, or erythropoietin as a co-medication. The rate of leukopenia was approximately the same as the rate of anemia. The clinical significance of RBV dose reductions with respect to SVR in the post-LT setting has to be awaited. In non-LT patients, no significant impact on SVR has been observed.[32] Our findings exceed the rates of side effects from published trials,[4,6,29] but they are comparable to the results of the French early access program: in an interim analysis presented at the 2012 EASL annual meeting, which was a real-life analysis of a difficult-to-treat group of patients consisting of pretreated patients with cirrhosis, hematological side effects were also common, and 56% of TVR-treated patients needed the administration of erythropoietin because of anemia.[27] Additionally, all patients in the French post-LT cohort required erythropoietin because of anemia.[28] However, these results may mirror the clinical prerequisites of these difficult-to-treat groups of patients. In the French early access cohort of pretreated cirrhotic patients, more cirrhosis-specific pathological effects may have played a role, whereas in the french post-LT cohort and our group of patients, the higher rates of hematological side effects are probably more the result of the combined myelotoxicity of immunosuppressants, PEG-IFN, and TVR.

In conclusion, triple therapy with TVR has promising antiviral efficacy in LT patients with respect to treatment weeks 4 and 12. The management of drug-drug interactions during TVR exposure is a therapeutic challenge, but they may be more controllable if CSA is used as the main immunosuppressive agent.

Triple therapy has an acceptable safety profile, although the treatment is quite intense with respect to cost and time. Therefore, we recommend that this therapy be conducted only by expert transplant hepatologists with strict surveillance of the patients because of the potential development of severe side effects.

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