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MINIREVIEWS

Hepatitis C virus reinfection after liver transplant: New chances and new challenges in the era of direct-acting antiviral agents

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Abstract

The first interferon-free regimens have been approved for the treatment of patients with chronic hepatitis C virus (HCV). In the liver transplant (LT) setting, these regimens are expected to have an important effect, because graft loss due to HCV recurrence is a serious problem after LT. The response to the hitherto conventional treatment with pegylated interferon and ribavirin is poor. The significantly better response rates achieved with boceprevir-based and telaprevir-based triple therapy have led to better graft and patient survival rates, but severe drug interactions with immunosuppressants limit the feasibility of this therapy for LT patients. With the approval of sofosbuvir in January 2014, of simeprevir in May 2014, and of daclatasvir in August 2014, three antiviral agents are now available and promise to be applicable without relevant adverse effects or negative interactions with immunosuppressants. Thus, 2014 marks the beginning of a new era of treatment options for HCV recurrence after LT. Although safety and efficacy studies of several interferon-free regimens for patients with HCV recurrence after LT have achieved good preliminary results, reports of clinical experiences with LT patients are scarce. The lack of randomized studies, the small number of enrolled and carefully selected patients, and the heterogeneity of these studies make the results questionable. Real-life experiences are eagerly awaited so that clinicians can estimate the usefulness and the pitfalls of these new regimens. Additionally, the high costs of these agents may limit their accessibility for many patients. The aim of this review is to summarize the current experience with and the expectations of the new direct-acting antiviral agents for LT patients.

Key words: Hepatitis C virus; Liver transplant; Interferon; Sofosbuvir; Simeprevir; Daclatasvir

Core tip: In the liver transplant (LT) setting, graft loss due to hepatitis C virus (HCV) recurrence is a serious problem after LT. The former conventional treatment with pegylated interferon and ribavirin is unsatisfying, due to poor response rates and tolerability. With the first interferon-free regimens that are currently being approved for the treatment of patients with chronic HCV, 2014 marks the beginning of a new era

of treatment options for HCV recurrence after LT. This review summarizes the current experience with and the expectations of the new direct-acting antiviral agents in the setting of LT.

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LIVER TRANSPLANT IN THE SETTING OF CHRONIC HCV INFECTION

Chronic hepatitis C virus (HCV)-induced end-stage liver disease, with or without hepatocellular carcinoma, is still the leading indication for liver transplant (LT), and reinfection of grafts by HCV is the main cause of allograft loss[1,2]. Most patients experience recurrence of HCV infection after LT, and such recurrence can be associated with substantially accelerated cirrhosis of the graft in as many as 30% of patients[3,4]. A subgroup of patients experience fibrotic cholestatic hepatitis (FCH), a severe and extremely aggressive form of HCV recurrence characterized by rapid progression to graft failure and death. Once cirrhosis develops, the annual risk of hepatic decompensation is approximately 40%, and 10% to 25% of patients will die or require retransplantation within 5 years after the first LT[5]. Unfortunately, the outcome of patients undergoing re-transplantation is poor, and most transplant centers are reluctant to offer a second LT for patients with cirrhosis of the graft due to HCV reinfection[6,7].

The shortage of donor organs, in conjunction with the accelerated progression of HCV in LT patients, emphasizes the need for effective clinical strategies aimed at treating or preventing HCV recurrence after transplant. Three approaches have been described, according to the timing of treatment: antiviral therapy before LT, which is appropriate only for patients with compensated cirrhosis; preemptive treatment after LT[8]; and treatment of an established reinfection[9]. Thus, after transplant, HCV patients can be treated either immediately with a preemptive approach or with a recurrence-based approach when liver damage is diagnosed. The advantages of preemptive or early treatment after transplant are low serum HCV-RNA levels and no substantial damage to the graft, as determined by histologic studies[10]. Although these factors are positive predictors of a favorable outcome, this therapeutic approach has been difficult to manage because the combination of pegylated interferon (PegIFN) and ribavirin (RBV) is associated with poor tolerability and reduced efficacy[5]. Therefore, the preferred approach to date has been to delay antiviral treatment until histological evidence establishes a diagnosis of HCV-related chronic hepatitis after transplant.

It has been reported that the presence of substantial portal tract fibrosis or of portal hypertension one year after LT are predictors of a higher risk of clinical decompensation and death; therefore, these characteristics help determine which patients urgently need treatment[11]. For patients with FCH, meaning a severe recurrence of HCV early after transplantation, antiviral therapy would be life-saving; however, previous treatment options were unable to eradicate HCV in most cases, with the deleterious consequences of graft loss and death.

PREVIOUS THERAPEUTIC STRATEGIES

Since the discovery of the HCV in 1989[12], the development of effective therapeutic strategies has been hampered by the unavailability of cell-culture and small-animal models for investigating the virus. During the last decades, therapeutic approaches remained limited to unspecific IFN-based regimens with insufficient efficacy. Early trials of IFN monotherapy achieved sustained virologic response (SVR) in fewer than 10% of cases[13]. The introduction of combination therapy with RBV and IFN and the modification of IFN to PegIFN, which can be administered weekly and is associated with improved pharmacokinetics (PK), resulted in higher SVR rates[14]. The PegIFN and RBV dual combination treatment was the standard of care for all HCV genotypes for about 10 years. For many chronically infected patients, this treatment regimen fails to eradicate HCV and is associated with additional adverse effects, and it is even less efficacious for LT patients. The overall rates of SVR with PegIFN plus RBV are low, ranging from 30% to 40% across various reports[5,15]. These poor virologic response rates were mainly due to a high frequency of treatment discontinuation and also dose reduction which became necessary because of poor tolerance or adverse effects[16]. Moreover, as LT recipients are susceptible to hematologic toxicities, especially anemia, RBV dose reductions and the use of erythropoietin are common. Hematologic toxicity necessitates a dose reduction for nearly 70% of patients and early discontinuation of treatment for nearly 30%[16-18]. Moreover, some reports indicate that antiviral therapy may increase the risk of acute graft rejection[19]. The risk of rejection for LT patients ranges from 5% to 10%[20]. However, the probability of survival for patients with SVR after LT is clearly better than that for patients who do not respond to therapy[21].

In May 2011, the first-generation protease inhibitors (PIs), boceprevir (BOC) and telaprevir (TLV), broke this paradigm. The United States Food and Drug Administration approved these drugs for use in association with PegIFN and RBV[16,22]. Both PIs inhibit the same viral protein (NS3/4A) that is crucial for viral replication, and both are active against GT 1

but not against other HCV genotypes. For the other HCV genotypes, PegIFN plus RBV remained the standard of care. Several studies have evaluated the feasibility of these regimens for several hundred LT patients with HCV recurrence[23-26]. About one-third of the patients received BOC and the majority was treated with TLV. Most patients had advanced-stage fibrosis, and approximately half had received at least one previous course of antiviral treatment. The reports described rapid virologic response rates from 53% to 67%, and SVR rates 12 wk after the end of therapy from 48% to 62%[27,28]. While these results were quite encouraging in terms of efficacy, the administration of direct-acting antiviral agents (DAAs) after LT was associated with serious concerns about tolerability and the risk of severe adverse events[24-26]. Indeed, the bone marrow-suppressive effect of TLV and BCV could amplify the anemia, neutropenia, and thrombocytopenia induced by RBV and PegIFN[29]. In addition, TLV and BCV cause severe dermatologic effects, such as generalized pruritus and anorectal disorders[30].

In addition, drug-drug interactions are a serious obstacle of the new antiviral agents. First-generation PIs (TLV, BCV) are not only processed by but also inhibit the CYP3A4 isoenzyme, which is involved in the metabolism of most drugs, including the calcineurin inhibitors (CNIs) cyclosporin A (CSA) and tacrolimus (TAC). BCV has been shown to cause a 2.7-fold increase in the area under the curve (AUC) of CSA and a 17-fold increase in the AUC of TAC, whereas TLV causes a 4.6-fold increase in the AUC of CSA and a 70-fold increase in the AUC of TAC[31,32]. Considering the narrow therapeutic range of CSA and TAC, dose adjustments are of imminent importance, and these drugs must be very closely monitored when they are combined with PIs[27,28,33].

Although the first-generation PIs achieved a substantial improvement in terms of efficacy, their described disadvantages and the fact that IFN is still necessary limit the patient population for which this treatment strategy is appropriate. For particular groups of patients, IFN-based regimens are contraindicated or not applicable or repeatedly failed. Those patients depend on the development of IFN-free regimens.

In this respect, the recent introduction of second-generation DAAs, including PIs, polymerase inhibitors, and nonstructural protein inhibitors has initiated a new era of HCV treatment.

FUTURE THERAPEUTIC STRATEGIES: NEW DAAS AND IFN-FREE REGIMENS AFTER LT

For decades, HCV has successfully escaped from all efforts to generate more efficient drugs, although research efforts have been intense[34]. Viral replication *in vitro* or in small-animal models could not be achieved, and functional studies were limited to chimpanzees[35-37], what caused an important drawback to DAA development. The ultimate breakthrough for HCV drug development may be dated to establishment of the HCV replicon system, what was not earlier that 1999[34,38]. HCV subgenomes, which compose the non-structural proteins NS3-NS5 linked to a selectable marker, can efficiently replicate *in vitro*. A few years later, a full-length isolate of HCV became available which can produce infectious viral particles *in vitro*[34,39]. The resulting improvement in the understanding of the viral life cycle opened the doors for the development of the first-generation DAAs. Drug development was further supported by structural biology, which has provided high-resolution images of the structures of the virus, revealing additional crucial drug targets, such as NS3, NS5A, and NS5B. These images have allowed modelling of interactions between specific replication inhibitors and their targets[34,40,41].

With the advent of the NS5B polymerase inhibitor sofosbuvir (SFV)[42], the NS3 PI simeprevir (SMV)[43], and the NS5A replication inhibitor daclatasvir (DCV)[44], three "second-wave" DAAs are now available and promise to be appropriate for LT patients, without severe adverse effects or negative interactions with immunosuppressants.

However, reports of trials of IFN-free DAA combinations in patients after LT are still scarce. The combination of SFV and RBV was the first IFN-free regimen to be tested for treating HCV recurrence in a compassionate use program[45]. Preliminary results of the use of this combination for 24 wk with recurrent HCV hepatitis after LT report a high overall SVR rate of almost 80%. The treatment is not only well tolerated but did also achieve a significant improvement in liver function tests and encephalopathy as well as decompensation[16,46]. Importantly, no clinically significant interactions with common immunosuppressants were observed and no episodes of rejection occurred. Overall, the preliminary analysis of experiences with patients in these programs indicate that a SFV-based regimen can inhibit HCV replication in most patients. This impairement of viral load goes in line with an improvement in clinical parameters and condition in the majority of those patients. However, although these results are already very encouraging, longer follow-up periods and a larger number of patients are needed to assess the impact on disease progression[46]. In addition, SFV and RBV have been successfully used to treat FCH[47,48].

In a phase 2, open-label study, 61 patients who were on the waiting list for liver transplant due to HCV cirrhosis were treated with SFV and RBV for up to 48 wk. At the time of LT, 43 patients had HCV RNA below detection levels and 30 patients (70%) had still a negative viral load 12 wk after LT. The most frequently reported adverse events were fatigue, headache and anemia[49].

To date, only a few reports reflect experiences

with the use of other IFN-free regimens other than SFV and RBV for LT patients. Fontana *et al* reported the first patients who were successfully treated with a combination of DCV and IFN or DCV and SFV for 24 wk combatting a severe HCV recurrence after LT[50,51]. In the meantime, several multicentric clinical trials are ongoing to assess the safety and efficacy of several oral DAA combinations for patients with HCV recurrence: (1) ABT450/ABT267/ABT333/RBV for 24 wk (NCT01782495); (2) SMV/DCV for 24 wk (NCT01938625); (3) SFV/RBV for 24 wk (NCT01779518); and (4) SFV/LDV/RBV for 12 or 24 wk (NCT01938430).

It is expected that the approval of these combinations for the use after LT will dramatically change the management and outcome of LT patients[16]. First summary reports implement suggestions for IFN-free treatment regimens for LT patients[52,53]. However, there remain several challenges and uncertainties for the use of IFN-free regimens to treat patients with very aggressive forms of hepatitis C (such as FCH), which occurs very early after transplantation. The pitfall may be the early setting while patients are still taking high doses of immunosuppressants[16]. Therefore, this period bears the risk of opportunistic infections[54]. Moreover, patients are during that period are often recovering from or being treated for surgical complications.

Indeed, the potential interaction of DAAs with CSA, TAC, and other immunosuppressants is an important issue for LT patients. Fortunately, most anti-HCV therapeutics which currently in phase 3 development have been successfully tested for potential interactions with CSA and TAC, at least in healthy volunteers. Co-administration studies in healthy volunteers found no clinically significant interactions with CSA or TAC[16,51].

Another common feature of LT patients is renal failure. Most patients exhibit a low glomerular filtration rate (GFR) because of previous renal damage that is aggravated by the long-term use of CSA or TAC[55]. In some cases, dose adjustments may be necessary and some compounds like SFV may be excluded from application if the GFR is lower than 30 mL/min.

A further issue that requires particular attention is the usually high viral load in patients who underwent LT, most likely due to the immunosuppression[56]. Exorbitantly high viral loads may well be a prerequisite for the selection of drug-resistant strains that may result in a virologic relapse if the appropriate combination of DAAs is not used. Therefore, after LT, resistance testing may become a necessary tool in the choice of the appropriate antiviral combination for the benefit of treatment efficacy and patient outcome[57].

TREATMENT BEFORE OR AFTER LIVER TRANSPLANT?

Treatment of patients while before liver transplant or while they are awaiting LT, respectively, may have several advantages. From the experiences with successful therapy of Hepatitis B, improvement in liver function may also be awaited for HCV clearance, and LT may become unnecessary in some cases. However, safety data and pharmakokinetics are not available for all compounds when administered to patients with cirrhosis classified as Child-Pugh B or C. Early reports suggest that deterioration of liver function is slightly accelerated after the administration of SFV/DCV to patients with decompensated cirrhosis after LT[58]. These observations suggest that treatment immediately after LT may be the better strategy for decompensated and severely sick patients.

Currently still a problem concerning patients awaiting LT is the uncertainty of treatment duration, because the length of time that a patient must remain on the waiting list cannot be predicted[16]. Though we can anticipate that, in the near future, all patients awaiting LT will receive successful treatment with the opportunity to receive LT after clearance of the virus, given the historical course of HBV.

Concerning treatment of HCV infection after LT, a few issues remain to be solved. Safety data as well as PK analyses are needed for this special patient population, particularly for those patients with advanced graft damage.

As well, drug-drug interaction studies are crucial because of the metabolism of CSA and TAC and a therapeutic range which is considerably narrow. This accounts not only for interactions with immunosuppressants but also with other commonly used drugs. Last but not least, a high barrier to resistance is also relevant for the use of direct-acting antivirals, particularly when high serum levels of HCV-RNA are observed[16].

CONCLUSION

Liver transplant due to HCV is a yet unmet challenge and a public health burden. Current developments predict a fundamental change of this situation: a large patient population for whom IFN-based treatment regiments are contraindicated, will now achieve access to potent antiviral therapies. While the use of novel DAA-based regimens in sufficient time before LT will prevent reinfection of the graft with HCV and avoid the need for retransplantation, the successful treatment of already recurred graft infection and damage in immunosuppressed patients after LT will pave the way to make a retransplant feasible. Most importantly, an early enough treatment of HCV patients on the waiting list will stabilize liver function with the consequence that LT will be dispensable in those individuals and HCV-related end stage liver disease can be expected to disappear from the transplant waiting list in the near future.

However, the efficacy of DAAs applied after LT in terms of SVR cannot yet be quantified, nor has their

adverse-event profile been ascertained for patients who have undergone LT. In addition, the potential predictors of SVR have not yet been identified. However, the absence of drug- drug interactions between CNIs and DCV, SMV, and SOF, in combination with the so far reported significantly improved SVR rate achieved with these DAAs, offers a promising perspective. Given the potential clinical benefits, more extensive and reliable clinical data about the effects of these new potent HCV inhibitors on patients with recurrence of HCV infection after LT are urgently needed.

One of the remaining difficulties with these new regimens is the huge increase in treatment costs[42]. Affordability could be the pacemaker to set up strategies for personalization of treatment in areas of the world with economic limitations and also in selected patient populations. Some old but in certain cases sufficiently effective regimens using IFN-based regimens may find a niche in those patients with a history of several failed DAA regiments or who harbor multiple resistance-associated variants. While we experience the dusk of IFNs, these substances might stay advantageous for HCV therapy in consideration of features like absence of viral resistances, comparatively low costs and avoidance of drug-drug interactions in patients who are reliant on various concomitant medications.

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