Antivirals & Antiretrovirals

Boceprevir and Calcineurin Inhibitors – is there a Role for Treating Hepatitis C Recurrence after Liver Transplantation?

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Cirrhosis from Hepatitis C (HCV) remains the leading indication for liver transplantation in the United States with recurrent disease leading to cirrhosis in 42% of patients by 5 years post-transplant [1]. Aspegylated interferon (PIF) and ribavirin (RBV) are only effective in approximately 30% of patients with recurrent HCV genotype 1, this has led to recurrent HCV emerging as an important but controversial indication for retransplantation. On the other hand, the approval of protease inhibitors (PI's) for the treatment of pre-transplant patients with HCV genotype 1 in 2011 has rapidly transformed our management of this ubiquitous disease [2]. Sustained viral response (or 'cure') has increased from approximately 40% with the previous regimen of PIF and RBV to at least 65% with the addition of PI's. The natural corollary of the dramatic SVR's in pre-transplant patients is to examine whether there is a role for PI's in post-transplant recurrent HCV. However, according to the manufacturers' package insert, PI's such as boceprevir and telaprevir , are contraindicated in liver transplant recipients as they inhibit cytochrome P450 3A4 and 3A5(CYP3A4/5) which metabolize Cyclosporine (Csa) and Tacrolimus (Tac), leading to toxic and potentially life-threatening levels of these drugs [3,4]. This was demonstrated in anopen-label, single sequence study on 10 healthy volunteers in which the co-administration of telaprevir with either Csa or Tac led to a 4.6 fold rise in Csa and a 70 fold rise in Tac [5].

These concerns with telaprevir and CNI's were echoed in a recent study examining the pharmacokinetic interaction between boceprevir and CNI's [6]. This open-label, fixed sequence study was divided into 2 parts. In part 1, which was designed to study the effect of boceprevir on Csa pharmacokinetics, 10 healthy subjects received single dose Csa (100 mg) on day 1, single dose boceprevir (800 mg) on day 3 and concomitant Csa and boceprevir on day 4. After a wash-out period of one day, the subjects were administered boceprevir 800 mg three times a day for 7 days with single dose Csa (100 mg) on day 6. Due to the anticipated long half-life of Tac, part 2 was divided into 2 sections. In part 2A, which studied the interaction between boceprevir on Tac, 12 subjects received single dose Tac of 0.5 mg and after a wash-out period, boceprevir 800 mg three times a day was administered for 11 days with single dose Tac (0.5 mg) on day 6. In part 2b which studied the effect of Tac on boceprevir, 10 subjects received single dose boceprevir (800 mg) and 24 hours later received a second dose of boceprevir 800 mg with Tac 0.5 mg. Blood samples were obtained predose and at selected time points throughout the study for pharmacokinetic determination of Csa and Tac using high-performance liquid chromatography.

The coadministration of boceprevir with Csa increased the mean area under the concentration time curve from time 0-infinity (AUC_{inf}) from 188 ng.h/ml to 4870 ng.h/ml and the mean maximum observed concentration (C_{max}) of Csa from 388 ng/ml to 737 ng/ml. This was associated with an approximately 2 fold reduction in Csa clearance and a prolongation in Csa half-life from 11.3 hours to 15.7 hours in the presence of boceprevir. The concomitant administration of Tac and boceprevir increased the AUC_{inf} from 21.8 ng.h/ml to 345 ng.h/ml and the C_{max} levels from 0.8 ng/ml to 7.8 ng/ml. Boceprevir clearance was 18 times less following the coadministration with boceprevir. Although

Csa increased boceprevir AUC_{inf} and C_{max}, these elevations were not of clinical significance whereas these values were unchanged with the administration of Tac versus boceprevir administration alone.

Although this study reinforces the importance of the drug interactions between boceprevir and CNI's, there are several other important points which merit review. Firstly, this study was conducted in healthy subjects and not liver transplant recipients with recurrent HCV who may metabolize medications differently during the course of drug exposure as the presence of recurrent HCV or its eradication can influence drug metabolism [7]. Liver transplant recipients are also exposed to several other medications which may affect boceprevir metabolism independent of CNI's. Thirdly, CYP3A4/5 polymorphisms in the healthy subjects may have also influenced the metabolism of CNI's in the presence of boceprevir but this was not obtained prior to the study nor has this been extensively studied in liver transplant recipients with recurrent HCV.

Despite the manufacturer's warnings in the package insert and the significant concerns of the interactions between PI's and CNI's, clinicians have proceeded to treat recurrent HCV in the absence of evidence [8]. It would appear that these efforts should only be reserved for patients with advanced fibrosis in where retransplantation would not be an option or in fibrosing cholestatic HCV recurrence which is usually a pre-terminal event. Although the investigators reported that 82% of their patients who received boceprevir had at least stage 3 fibrosis, only 55% of their patients who received telaprevir had advanced disease which translates to 45% with non-advanced liver disease subjected to triple therapy. Erythropoietin was required in 90% of patients but fortunately other adverse events were kept to a minimum with complete viral response at 8 weeks achieved in 56% of boceprevir-treated patients and 70% of telaprevir-treated patients.

Despite the impressive results from this post-transplant study, the ends do not justify the means. We urgently need to use evidence-based data from prospective, randomized controlled studies conducted in liver transplant recipients with recurrent HCV before embarking on triple therapy. Desperate patients and their families must be thoroughly educated about the risks and benefits of triple therapy which remains experimental, unproven and potentially life-threatening and should

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only be considered for patients with progressive liver disease when no other options are available.

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