

Protease Inhibitors for Recurrent Hepatitis C after Liver Transplantation-When Less is More

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The approval of boceprevir and telaprevir, two protease inhibitors for hepatitis C (HCV) treatment earlier this year, was met with virtually universal optimism as the addition of these medications will lead to a significantly improved chance of viral eradication in HCV genotype 1 patients [1]. However, this enthusiasm is yet to be embraced by the liver transplant community primarily due to the interaction between protease inhibitors and calcineurin inhibitors such as cyclosporine and tacrolimus. Boceprevir and telaprevir inhibit cytochrome P450 3A which metabolizes cyclosporine and tacrolimus leading to elevated and potentially lethal levels of these calcineurin inhibitors [2,3].

This was confirmed in an important phase I, open-label randomized, single sequence study earlier this year by Garg et al. [4] which merits further review. In part A of the study, ten healthy volunteers were administered a single 100mg oral dose of cyclosporine followed by an 8 day washout period before they were administered a single 10mg dose of cyclosporine and either a single dose of telaprevir 750 mg or steady-state telaprevir 750mg every 8 hours. In part B, ten volunteers were administered a single dose of tacrolimus 0.5mg followed by a 14 day wash-out period before they were administered a single 0.5mg dose of tacrolimus with telaprevir 750mg every 8 hours. Blood samples were obtained throughout the study for pharmacokinetic assessment and analysis. The investigators reported that co-administration of telaprevir with cyclosporine and tacrolimus, respectively, led to increased cyclosporine by 4.6 fold and tacrolimus by 70 fold, levels that are toxic and life-threatening.

This important study has confirmed the concerns of many transplant hepatologists. Despite the study's findings, there were some important limitations, notably that it was conducted in healthy volunteers and not in liver transplant recipients with recurrent HCV. Extrapolating these results to a different patient population may be hard to justify. However, it seems more rather than less likely that HCV protease inhibitors should be prescribed with extreme caution in transplant patients-not only may drug metabolism be different from healthy volunteers but transplant recipients are also exposed to a variety of other medications that may interact with protease inhibitors independent of calcineurin inhibitors.

The concerns with HCV protease inhibitors were eloquently outlined by Michael Charlton, MD in an accompanying editorial this year [5]. Before we prescribe these medications, we need to inform patients and their families the following:

- (a) Treatment is experimental as there are no studies in liver transplant patients
- (b) Side effects may include organ failure and death from severe calcineurin toxicity
- (c) Hepatic allograft rejection is a possibility as the dose and frequency for either calcineurin inhibitor has yet to be established

- (d) Drug-Drug interactions between protease inhibitors and other medications used in transplant recipients are not fully recognized
- (e) Only physicians well-versed with the management of liver transplant recipients and drug-drug interactions should care for these patients
- (f) Treatment should only be reserved for patients with aggressive histological evidence of recurrent HCV in an attempt to prevent retransplantation [6].

Until the appropriate randomized trials are performed, transplant physicians should be extremely wary of prescribing these medications for patients with recurrent HCV. Human nature is such that it is inevitable that these medications will be used (or already have), in some cases probably appropriately as in patients where retransplantation or even re-retransplantation is to be avoided or contraindicated. Under these circumstances, adhering to the above check-list may lessen morbidity and mortality in this vulnerable group of patients.

References

1. Ferenci P, Reddy KR (2011) Impact of HCV protease-inhibitor-based triple therapy for chronic HCV genotype1 infection. *Antivir Ther* 16: 1187-1201.
2. Boceprevir (Victrelis) US Package Insert 2011.
3. Telaprevir (Incivek) US Package Insert 2011.
4. Garg V, Van Heeswijk R, Eun Lee J, Alves K, Nadkarni A, et al. (2011) Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. *Hepatology* 54: 20-27.
5. Charlton M (2011) Telaprevir, boceprevir, cytochrome P450 and immunosuppressive agents-a potentially lethal cocktail. *Hepatology* 54: 3-5.
6. Limaye A, Firpi RJ (2011) Management of recurrent hepatitis C after liver transplantation. *Clin Liv Dis* 15: 845-858.

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