Victory and defeat at Heraclea – Treating hepatitis C infection following liver transplantation with telaprevir and boceprevir

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HCV associated liver disease continues to be the most common indication for liver transplantation in the West. Although the impact of HCV infection varies substantially between recipients, allograft failure secondary to recurrence of HCV infection is the most frequent cause of death and graft failure in HCV infected recipients. Attenuating the impact of HCV on posttransplant patient and graft survival has been a critical priority for transplant physicians and their patients. In this edition of the Journal of Hepatology Duclos-Vallée et al., report the results of a multicenter study of 37 liver transplant recipients (male: 92%, age 57 ± 11 years), who were treated with PEG interferon, ribavirin and boceprevir (n = 18) or telaprevir (n = 19) for recurrence of HCV infection following liver transplantation. The indication for therapy was progressive HCV recurrence (fibrosis stage ≥F2 (83%) or fibrosing cholestatic hepatitis (16%). Eighteen patients were treatment-naïve, five were relapers and 14 were non-responders to prior dual therapy after LT. The patient population was, by and large, typical of recipients with post-LT HCV infection who are considered for boceprevir and telaprevir based antiviral therapy. The main finding of the study by Duclos-Vallée et al., is that a sustained virological response (SVR) at 12 weeks after treatment discontinuation was observed in 20% and 71% of patients in the telaprevir (TVR) and boceprevir (BOC) groups, respectively, for an overall SVR rate of 50%. While a study with patients in the telaprevir (TVR) and boceprevir (BOC) groups, treatment discontinuation was observed in 20% and 71% of those with the most severe recurrence of HCV did not respond to antiviral therapy in this study, it is entirely plausible that there will be no net survival benefit to treating liver transplant recipients with BOC or TVR in the medium term (the likelihood of mortality/graft loss due to HCV is likely to be highest among the FCH/cirrhosis patients, who had a low SVR rate). The frequency of SAEs greatly limited the potential efficacy posttransplant antiviral therapy in the study by Duclos-Vallée et al., with only half of the ~50% of patients who discontinued treatment doing so for virological nonresponsiveness/breakthrough, the remainder...
Table 1. Empiric recommended dosing strategies of concomitant protease inhibitors and immunosuppressants when both initiating and discontinuing protease inhibitor therapy. Empiric dose changes should be done in conjunction with therapeutic drug monitoring.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Drug exposure effect</th>
<th>At boceprevir initiation</th>
<th>At boceprevir discontinuation</th>
<th>At telaprevir initiation</th>
<th>At telaprevir discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>CYP450 3A4 Inhibition</td>
<td>↑</td>
<td>↑ 50%</td>
<td>↑ 100%</td>
<td>↓ 75%</td>
<td>↑ 100%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>CYP450 3A4 Inhibition</td>
<td>↑</td>
<td>↓ 75%</td>
<td>↑ 100%</td>
<td>↓ 90%</td>
<td>↑ 100%</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>CYP450 3A4 Induction</td>
<td>↑</td>
<td>Black box warning for use in liver transplant recipients. Recommend everolimus if mTOR inhibitor indicated.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>CYP450 3A4 Inhibition</td>
<td>↑</td>
<td>↓ 50%</td>
<td>↑ 100%</td>
<td>No published data. Likely ↓ 75%</td>
<td>↑ 100%</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>No published interaction</td>
<td>No change known</td>
<td>No change known</td>
<td>No empiric dose adjustments necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No published interaction</td>
<td>No change known</td>
<td>No change known</td>
<td>No empiric dose adjustments necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>No published interaction</td>
<td>No change known</td>
<td>No change known</td>
<td>No empiric dose adjustments necessary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dying or experiencing adverse events severe enough to stop antiviral treatment. A third lesson of the study by Duclos-Valleé et al., is that full realization of the potential benefit of BOC and TVR based posttransplant antiviral therapy requires minimisation of the side effects of these agents and those of peginterferon and ribavirin. The high frequency of infections and renal insufficiency suggests overexposure to calcineurin inhibitors. This is despite effective CNI trough level management through dose adjustments in anticipation of in response to the introduction of the cytochrome P450 inhibitors boceprevir and telaprevir. Renal insufficiency and life threatening infections despite stable CNI levels is a consistent emerging theme of posttransplant antiviral therapy. A thorough appreciation of the impact of post-LT antiviral therapy on the pharmacokinetics of immunosuppression agents is essential to achieving optimal safety and efficacy.

The cytochrome P450 (CYP) enzyme system is responsible for drug metabolism via oxidation in the liver and intestines allowing drugs to be eliminated into the bile or urine. The CYP 3A4 iso- enzyme is used by more than 50% of approved medications for elimination from the body [1]. Protease inhibitors, such as boceprevir (BOC) and telaprevir (TVR), in addition to being potent inhibitors of the CYP 3A4 enzyme leading to many potential drug-drug interactions (DDI), are also (TVR > BOC) inhibitors of the CYP 3A4 enzyme, such as boceprevir and telaprevir. Renal insufficiency and life threatening infections despite stable CNI levels is a consistent emerging theme of posttransplant antiviral therapy. A thorough appreciation of the impact of post-LT antiviral therapy on the pharmacokinetics of immunosuppression agents is essential to achieving optimal safety and efficacy.

The major portion of whole blood CsA and TAC is sequestered in erythrocytes, with hematocrit known to be inversely related to plasma concentrations of CNIs [11]. Due to RBV induced hemolysis a shift of the erythrocyte-bound CsA fraction to plasma will hepatic function. As HCV can decrease CYP function, increasing calcineurin inhibitor concentrations by approximately 30% [4,5], pharmacokinetic effects in LT recipients with HCV infection may be more pronounced than those seen in healthy volunteers. Tacrolimus doses as little as 0.5 mg per week are adequate to maintain therapeutic concentrations when given with the protease inhibitor combination of lopinavir/ritonavir [6]. In healthy volunteers TVR can increase tacrolimus concentrations as much as 70-fold and cyclosporine concentrations 4.6-fold [7], while BOC increases tacrolimus concentrations 17-fold and cyclosporine 2.7 fold [8]. Based on the known effects of BOC and TVR, CNI and mTOR doses should be decreased empirically when starting protease inhibitor therapy and consequently increased when protease inhibitor therapy is discontinued. Sirolimus, and everolimus are also known substrates of CYP 3A4 and P-gp. No published data exist describing the DDI between everolimus and TVR, however everolimus clearance is decreased by 52%, when administered with BOC [9]. As sirolimus carries a black box warning for use in liver transplantation [10], it may be wise to avoid this agent altogether in patients receiving TVR or BOC. Consideration might be given to everolimus use in place of sirolimus if an mTOR inhibitor is indicated. The shorter half-life of everolimus may make management of drug-drug interactions easier than sirolimus.

DDI can be significant in transplant recipients as the calcineurin inhibitors, mTOR inhibitors, and a multitude of other medications are transported by P-gp and/or metabolized by the CYP 3A4 enzyme. It is important to screen concomitantly administered medications other than the CNIs and mTORs for potential DDI or contraindications. Common CYP 3A4 substrates include azole antifungal agents, HMG-CoA reductase inhibitors (statins), methadone, and many others. Increasing the frequency of therapeutic drug monitoring of immunosuppressants and other concomitant medications is imperative when both starting and stopping protease inhibitors.

Finally, as all CNI trough levels are measured in whole blood, trough levels will not accurately reflect the biologically active (immunosuppressive and nephrotoxic) free CNI trough levels. The major portion of whole blood CsA and TAC is sequestered in erythrocytes, with hematocrit known to be inversely related to plasma concentrations of CNIs [11]. Due to RBV induced hemolysis a shift of the erythrocyte-bound CsA fraction to plasma will...
occur. Anemia will be exacerbated by peginterferon and BOC induced bone marrow suppression. In the context of progressive, ubiquitous and frequently severe anemia relying on whole blood level monitoring may not be safe. As free CNI level monitoring is not widely available, consideration should be given to adjusting target CNI whole blood trough levels downward in the context of a falling hematocrit.

On being congratulated for his victory over the Romans at Heraclea, King Pyrrhus, whose army had suffered irrecoverable casualties, replied that one more such victory would utterly undo him. The report by Duclos-Vallée et al., should serve to remind us of the possibly Pyrrhic nature of our battle with posttransplant HCV infection. We eagerly await the advent of HCV therapies that are more effective and more easily tolerated than those that incorporate BOC and TVR. For patients with mild recurrence, waiting may be more prudent than joining the battle.

Conflict of interest

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References