ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Use of Protease Inhibitors in Liver Transplant Recipients


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G&H What is the currently approved therapy for treatment of hepatitis C virus infection in liver transplant recipients? How effective is such therapy?

GLD/JGO Hepatitis C virus (HCV) infection persists in all viremic HCV-infected persons who undergo liver transplantation, and reinfection is a major problem. Although recurrence can occasionally be severe, as in cases of fibrosing cholestatic hepatitis, recurrence typically results in less severe but varying degrees of inflammation of the graft. However, fibrosis progresses much faster in patients who have undergone liver transplantation than in nonimmunosuppressed individuals. Indeed, 20–40% of liver transplant recipients progress to cirrhosis within 5 years of transplantation, and graft failure ensues within 12 months in approximately 40% of these cases. Thus, curative antiviral treatment could have a major positive impact in patients with progressive liver injury. Unfortunately, pegylated interferon and ribavirin are poorly tolerated in this group, cytopenia is problematic, and sustained virologic response (SVR) occurs in fewer than 30% of patients who attempt therapy.

G&H How are liver transplant recipients different from HCV-infected patients who have not undergone transplantation?

GLD/JGO Although patients who have undergone liver transplantation are often highly motivated, treatment of this group is difficult and labor-intensive for several reasons. Liver transplant recipients tend to have higher viral loads, more pronounced cytopenia, and some degree of renal insufficiency. All of these factors contribute to more frequent dose reductions, greater need for use of growth factors such as erythropoietin and filgrastim (Neupogen, Amgen), and lower response rates. In addition, many of these patients have already failed antiviral therapy before they undergo transplantation.

G&H Do these factors alter clinicians' therapeutic goals for HCV treatment in liver transplant recipients?

GLD/JGO No, the goal of therapy for a liver transplant recipient is the same as for any HCV-infected individual: namely, viral eradication. Viral suppression in the absence of complete viral eradication does not provide a documented benefit in liver transplant recipients. The only possible exception is in patients with fibrosing cholestatic hepatitis; viral suppression in these patients may improve liver function and be life-saving, even if SVR is not achieved.

G&H Why might protease inhibitors be considered to treat HCV infection in liver transplant recipients?

GLD/JGO Direct-acting antiviral agents—including the recently approved HCV protease inhibitors boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex)—can dramatically increase the chance of achieving SVR. This

increase is most apparent in patients who have the lowest response rates when treated with interferon and ribavirin alone, such as patients with high viral loads or previous nonresponders. For example, the addition of a protease inhibitor to standard therapy leads to a doubling of SVR rates in white patients, but it triples SVR rates in black patients (who have lower response rates when treated with interferon and ribavirin alone). Therefore, patients who are at the greatest disadvantage have the most to gain from the addition of a direct-acting antiviral agent.

G&H What are the risks associated with such therapy?

GLD/JGO First, it is important to mention that HCV protease inhibitors have not been studied in liver transplant recipients; as a result, the US Food and Drug Administration has not approved the use of protease inhibitors in such patients. Furthermore, in addition to the aforementioned obstacles associated with interferon and ribavirin therapy, there are a number of specific obstacles to using protease inhibitors in the liver transplant patient population. Most importantly, protease inhibitors are potent CYP3A4 and p-glycoprotein inhibitors, and they dramatically increase exposure to drugs that are metabolized by these pathways. For example, exposure to calcineurin and mammalian target of rapamycin (mTOR) inhibitors, the foundation of immunosuppression in transplant recipients, is dramatically increased when recipients receive protease inhibitors, making drug toxicity a real possibility.

G&H Are there any ways to reduce these risks?

GLD/JGO Clearly, if clinicians choose to treat liver transplant recipients, the levels of patients' calcineurin and mTOR inhibitors must be followed extremely closely, and the doses of these immunosuppressant drugs would need to be adjusted downward accordingly. In addition, the patient's medication list would need to be closely reviewed to ensure that no other drug-drug interactions occurred.

G&H Have there been any published cases of liver transplant recipients who received protease inhibitor therapy? What were the outcomes in these cases?

GLD/JGO A small case series by Mantry and colleagues was recently presented at the HEPDART 2011 meeting in Koloa, Hawaii. This series documented early experiences in post–liver transplantation patients who were treated with triple drug therapy. Of 7 patients, 4 patients experienced rapid virologic response (RVR), 2 patients did not achieve RVR but remained on treatment, and 1 patient experienced early virologic failure and stopped therapy. One patient died of sepsis with a negative viral load.

G&H What is the current consensus regarding the use of protease inhibitors in liver transplant recipients?

GLD/JGO Clearly, given the increased risk of progressive liver disease in liver transplant recipients, there is a great need for effective therapy, which may well include protease inhibitors. However, such treatment will be clinically challenging, with real dilemmas (dosing and drug-drug interactions) and risks of adverse events. Given clinicians' limited experience with protease inhibitor therapy in this population to date, it would be premature to make any specific recommendations regarding therapy.

G&H Would other new HCV drugs be subject to the same risks associated with protease inhibitors, or might future drugs be more suitable for use in liver transplant recipients?

GLD/JGO Certainly, side effects and drug-drug interactions will differ among the new compounds. Ideally, we would like medications with minimal side effects, more convenient dosing regimens, and fewer drug-drug interactions. However, such drugs are not available at this time.

G&H What further studies are needed regarding treatment of HCV infection in liver transplant recipients?

GLD/JGO Any new agents that are approved for treatment of HCV infection will need to be studied in liver transplant recipients. In the future, more potent drugs may allow eradication of virus in a very short period of time; such therapy might pave the way to clearing virus before or at the time of transplantation and avoid the problem of recurrence altogether.

Suggested Reading

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