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EDITORIAL

Microemulsion Cyclosporine With C_2 Monitoring and Tacrolimus in Liver Transplantation With or Without Hepatitis C Virus Infection

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The introduction of calcineurin inhibitors has improved graft survival in the last 25 years.[1-3] The superiority of tacrolimus over cyclosporine (CsA) was well established in preventing acute rejection and corticosteroid-resistant rejection from 3 large randomized trials after liver transplantation. However, these differences were studied with a conventional formulation of CsA and CsA monitoring with trough (C_0) concentrations.[4-6] In addition, in those three studies, the indication of hepatitis C virus (HCV)-related end-stage liver disease is relatively low: it accounts for more than 40% of liver transplantations in the United States.[7] It is now clear that C_2 monitoring of CsA better reflects the area under the concentration curve of the drug and has a better safety and efficacy profile in renal transplantation.[8,9] Also, the microemulsion formulation of CsA (CsA ME) provides more predictable area under the concentration curve, and day-to-day fluctuations in concentration are less common. In liver transplantation, diversion of bile affects the absorption of CsA, which is less affected with CsA ME formulation.[10-16]

In vitro studies have shown anti-HCV activity of CsA at higher concentrations.[17,18] Thus, several questions emerge. Does microemulsion formulation of CsA with C_2 monitoring provides better safety and efficacy in liver transplant patients as compared with tacrolimus? And is there any benefit of CsA ME with C_2 monitoring over tacrolimus in HCV-positive patients undergoing liver transplantation? Both of these questions are important to clinicians in order to provide the best possible options for their patients.

In a U.S. multicenter trial, Wiesner[19] showed that the survival benefit of tacrolimus over CsA was maintained even in patients who were HCV positive with up to a 5-year follow-up. Ghobrial et al.[20] reported the results of a retrospective data analysis of 190 CsA-treated and 132 tacrolimus-treated HCV-positive liver transplant recipients, with median follow-up of 22 months, and found no difference in patient or graft survival. In their study, conventional CsA and CsA ME were grouped together. A randomized study by Martin et al.[21] of 77 patients examined the difference between CsA-treated or tacrolimus-treated HCV-positive liver transplant recipients. Although HCV RNA viral load in the CsA group were higher, histologically diagnosed HCV recurrence rate and survival rate were not different. However, CsA dose was not based on C_2 monitoring. Similarly, Zervos et al.[22] reported the results of a prospective study of tacrolimus-treated HCV-positive liver transplant recipients (n = 25) with CsA ME–treated HCV-positive liver transplant recipients (n = 24) with a median follow-up of 14 months. They found an increased incidence of acute rejection with CsA ME compared with tacrolimus but did not find any difference in patient survival or graft survival. A prospective study conducted in Europe, which included more than 600 cases, found a benefit with tacrolimus over CsA ME.[23] However, in both studies, C_0 concentrations were measured.[22,23]

Obviously, immunosuppression appears to play an important role in the recurrence of HCV in the allograft. It is known that the use of anti-lymphocytic antibody and boluses of corticosteroids have a detrimental outcome.[24-26] A rapid change in immunosuppressive agents is also believed to be detrimental,[27,28] and the

Abbreviations: CsA, cyclosporine; HCV, hepatitis C virus; CsA ME, microemulsion formulation of CsA.

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role of mycophenolate mofetil has remained unclear.[29-31] Papatheodoridis et al.[32] have suggested that the use of triple-drug immunosuppressive agents has a detrimental effect. It could be that overall increased immunosuppression by adding mycophenolate mofetil may override its antiviral activity, if any. Filipponi et al.[33] prospectively studied basiliximab plus CsA and azathioprine, with or without corticosteroids, in HCV-positive liver transplant recipients (n = 140). An increased rate of rejections was observed without the use of corticosteroids, but this did not affect the recurrence of disease or survival.

It is important to examine the newly emerged questions that Levy et al. report in the current issue.[34] This consists of a multicenter, prospective, randomized trial comparing CsA ME therapy (with C_2 monitoring, n = 250) with tacrolimus therapy (C_0 monitoring, n = 245), which included 12 months' follow-up data. Initial results of this study were reported in the year 2004, with 6 months follow-up.[35] The population consisted of 173 patients with HCV infection (CsA ME n = 88, tacrolimus n = 85). The overall rate of rejection, patient survival, and graft survival were comparable. However, certain interesting findings have emerged. A total of 36% of CsA ME patients and 24% of tacrolimus patients withdrew from the study for adverse effects by 6 months. Also, 22% of patients randomized to CsA ME were receiving tacrolimus at 12 months, and 5% of patients randomized to tacrolimus were receiving CsA ME. Withdrawal rates in the CsA ME group for adverse events were markedly higher compared with those in the tacrolimus group, which the authors ascribe to unfamiliarity with C_2 monitoring. This may only be partially true because treatment failure under conventional CsA was higher compared with tacrolimus therapy in previously reported randomized trials.[4,5] Further, it was found that the overall rate of nephrotoxicity (based on serum creatinine levels) and that the need for treatment of hypertension or hyperlipidemia were similar. However, the rate of new-onset diabetes was higher with tacrolimus, although fewer patients had diabetes at the time of enrollment—49% for patients receiving CsA ME compared with 70% for patients receiving tacrolimus.

When we examine the data regarding HCV-positive liver transplant recipients, we find that although randomization was stratified on the basis of HCV status, genotype of HCV, serial HCV RNA viral load, and protocol, liver biopsy samples were unfortunately not studied prospectively. However, 14 patients (16.5%) died or lost their grafts while receiving tacrolimus (n = 85), compared with 5 patients (5.7%) in the CsA ME group (n = 88), which was statistically significant. As the author points out in the discussion, most of the deaths and graft losses occurred in the early posttransplantation period and were not associated with HCV recurrence. Also, the causes of graft losses from rejection, infection, hepatic artery thrombosis, and other causes unrelated to HCV recurrence were higher in the tacrolimus group compared with CsA. Also, 8 patients in the tacrolimus arm, as analysis suggests, died with a functioning graft, compared with 4 in the CsA ME group.

The marked disparity in outcome occurred in the early period of the trial, when the impact of HCV recurrence and its effect on survival are the least expected. Interestingly, the number of graft loss or deaths between 6 to 12 months' follow-up were the same in both groups. In that respect, the impression given in the paper by Levy et al. in this issue that CsA ME has a significant survival advantage over tacrolimus may be inappropriate. As the authors rightly points out, however, the need for prospective trials especially designed to study the outcomes of the HCV-positive population are extremely important to identify whether CsA ME (along with C_2 monitoring) has any advantage over tacrolimus.

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