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LETTER

Update on the clinical utility of once-daily tacrolimus in the management of transplantation

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Dear editor

The review by Posadas Salas and Srinivas of the clinical utility of once-daily tacrolimus formulations in the management of transplant patients[1] was timely and relevant. It is worth noting, however, the data were presented in a way that overlooked several key differences between two distinct once-daily tacrolimus formulations. These formulations differ in bioavailability, C_{max}, T_{max}, dose required to achieve target trough levels, and time to reach target trough. The specific formulation and dosing information of one product was detailed in this review (described as modified release 4 [MR-4]; Astagraf®, Astellas Pharma Inc., Tokyo, Japan), but no formulation or dosing details were provided for a very different once-daily tacrolimus formulation (LCP-Tacro™; Veloxis Pharmaceuticals A/S, Hørsholm, Denmark) for which a thorough review was recently published.[2] The latter product is currently approved in Europe and under review by the US Food and Drug Administration in the US. In presenting data in this review, the authors did not identify which product was investigated in each of the studies discussed. This could easily lead to misinterpretation of results or erroneous conclusions, ie, that both once-daily formulations are the same. In fact, a careful parsing of the data clearly demonstrates that they are not equivalent. Misunderstanding of this point could have a potentially serious impact on appropriate dosing, safety, and patient management in the post-transplant setting. Differentiation between the two products is needed to clarify what appear to be conflicting results of the studies presented in this review.

LCP-Tacro

To date, two Phase III non-inferiority studies have been published evaluating the efficacy of LCP-Tacro in kidney transplant recipients.[3,4] The first was an open-label, randomized trial evaluating conversion from twice-daily to once-daily LCP-Tacro in stable kidney transplant recipients and was detailed thoroughly by Posadas Salas and Srinivas.[3] The second, a double-blind, double-dummy, randomized, non-inferiority trial of LCP-Tacro versus twice-daily tacrolimus in 543 de novo kidney transplant recipients, was not included in this review.[4] The results of the 324-patient conversion trial and 543-patient de novo trial each individually demonstrated non-inferiority of once-daily LCP-Tacro to twice-daily tacrolimus with identical or lower rates of treatment failure.[3,4] These trial results stand in direct opposition to data from trials that evaluated the alternative once-daily formulation (MR-4) in which rates of biopsy-proven acute rejection (BPAR), or treated rejection, were increased, in some cases significantly so.[5–7] In one of these studies, the MR-4 formulation of once-daily tacrolimus failed to demonstrate non-inferiority.[5]

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Posadas Salas and Srinivas report results of a study that demonstrated rejection episodes requiring anti-lymphocyte therapy were more commonly seen among de novo kidney transplant patients treated with the MR-4 once-daily formulation of tacrolimus compared to twice-daily tacrolimus. They go on to note that about one-third of patients who received MR-4 had trough levels below target during the early post-transplant period (day 3 post-transplant). While the difference in rejection rate did not reach statistical significance, the authors note a trend toward higher mean tacrolimus levels in the twice-daily tacrolimus group who did not experience BPAR compared to those who developed BPAR. These data stand in contrast to data not presented by Posadas Salas and Srinivas, which demonstrate that in de novo kidney transplant patients treated with the LCP-Tacro once-daily formulation, therapeutic tacrolimus concentrations were achieved rapidly – with 66.5% of patients having a serum tacrolimus trough concentration of at least 6 ng/mL 24 hours after their first dose of LCP-Tacro.[8] LCP-Tacro-treated patients in this study experienced similar, though numerically lower, rates of BPAR compared to twice-daily tacrolimus at both 1 year and 2 years post-transplant.

Furthermore, pharmacokinetic (PK) differences are noteworthy between the two once-daily tacrolimus formulations. In contrast to data demonstrating the need for potentially higher total daily doses of tacrolimus when the MR-4 formulation is used,[5,9] LCP-Tacro has consistently demonstrated greater bioavailability and significantly lower total daily dose requirements compared with twice-daily tacrolimus (Prograf®, Astellas Pharma Inc.) in kidney and liver recipients and in both the de novo and conversion settings.[8,10–12] The Phase II study of 47 stable kidney transplant patients cited by Posadas Salas and Srinivas, reporting a 30% lower daily dosing requirement, evaluated the PK of LCP-Tacro after conversion from twice-daily tacrolimus,[11] and cannot be extrapolated to the MR-4 formulation.[10] Results of this study, as summarized in the review, were that patients taking LCP-Tacro had similar overall tacrolimus exposure (area under the curve) but with significantly lower C_{max} ($P<0.0001$), delayed T_{max} (1.8 hours for twice-daily versus 6 hours for LCP-Tacro, $P=0.0001$), lower peak-trough ratios ($P<0.0001$ on day 14, $P=0.0004$ on day 21), and less fluctuation ($P<0.0001$) compared with twice-daily tacrolimus.[10]

Based on the PK data presented in this response, the greater bioavailability and lower dose requirement are clinically relevant PK differences of the LCP-Tacro formulation compared with MR-4. The authors put forth the message that the PK profiles of once- and twice-daily tacrolimus suggest bioequivalence, yet available data for LCP-Tacro do not support this claim versus twice-daily or the MR-4 once-daily tacrolimus formulations. While no direct Phase III data comparing the two once-daily formulations have been published, Phase I data in healthy volunteers demonstrate that LCP-Tacro was 50% more orally bioavailable compared to the MR-4 once-daily formulation.[13] This difference could result in significantly different dose requirements and conversion factors, and it is vital for clinicians to understand these important differences to ensure safe use of these unique once-daily formulations of tacrolimus.

Conclusion

Without clarity on the specific once-daily tacrolimus formulation evaluated in each of the trials discussed in the review by Posadas Salas and Srinivas, it is difficult to reconcile potentially conflicting data.

A more complete review of the data regarding once-daily formulations clearly shows important differences between the MR-4 and LCP-Tacro once-daily tacrolimus formulations. These differences may have important clinical implications when selecting a once-daily tacrolimus to manage immunosuppression in transplant recipients.

Disclosure

The author has no conflicts of interest to disclose.

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Authors' reply

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Dear editor

We thank Dr Revollo for her careful reading of our paper and her thoughtful comment. Our review article presents an accurate and unbiased account of the results of several major studies on once-daily tacrolimus (whether MR-4 or LCP-Tacro) already published at the time of publication of our review article. The studies we reviewed were clearly referenced to reflect results obtained from analysis of either formulation. We were not able to include the results of Budde et al[1] in our review since this study was published at a later time.

Our effort reflects a conscious decision to point out the limitations of data as they pertain to newer once-daily tacrolimus formulations. Furthermore, we restricted our review to include, in the main, studies that had passed peer review. As such, abstracts and conference proceedings were exhibited in a very limited manner if at all. Unfortunately, the field of transplantation is congested with numerous studies conducted among normal volunteers and stable transplant recipients. Given this, extrapolation of data accrued from such studies to de novo transplant recipients or those populations at higher risk for immunologic events is not straightforward. Therefore, we employ a cautionary tone that implies a watchful expectancy of benefit from the newer tacrolimus formulations. We have also been very careful to not endorse one formulation over the other as the data just do not exist and experience needs to accrue in the marketplace.

Disclosure

The authors have no conflicts of interest to disclose.

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