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Letter to the Editor

Empirical or unconscious reduction of the secondary immunosuppressive drug concomitantly with intended calcineurin inhibitor reduced exposure to improve kidney graft function can be followed by antibody mediated rejections

To the Editor:

During the first years of the past decade, the progressive deterioration of glomerular filtration rates (GFR) in kidney allografts was mainly attributed to chronic calcineurin inhibitor (CNI) toxicity (1).

Shortly thereafter, as CNI tapering became more common, an epidemic outbreak of antibody-mediated rejections (AMR) began, mainly in its chronic form. A decade later, chronic AMR had replaced CNI toxicity as the main culprit of graft failures (1).

The causes of AMR were suspected to be either poor immunosuppressive (IS) treatment compliance in patients or iatrogenic IS modifications by physicians, especially regarding minimization or withdrawal of CNI (1).

However, little to no emphasis has been put on the secondary IS agent, especially mycophenolic acid (MPA) derivatives, maybe because most physicians could consider that MPA behaves in a "binary way," granting all of its benefits regardless of the prescribed doses and that a decreased dose is immunologically innocuous. This, as I will try to argue, may not be the case.

Mycophenolic acid compounds show poor and nonlinear correlations between doses, drug exposures and pharmacodynamics (2). Moreover, MPA exposure decreases as patients become fatter (2) and as attending transplant physicians reduce the clinical trial tested and FDA approved dose of 2 g/d of mycophenolate mofetil (MMF) or 1.44 g/d of sodium MPA, be it due to empirical reasons or because of adverse events, to even less than half 12 months after the transplant (3). All of these factors certainly can threaten an adequate MPA drug exposure and IS effect.

After the attention given to CNI toxicity (1), the tendency has been to attempt to reduce CNI exposure, although with less consideration towards maintaining the approved MPA dosing.

However, several prospective observational trials have shown that MMF doses are inversely correlated to both histological chronicity indexes in graft biopsies and GFR (4, 5). Furthermore, lower MMF doses can also deteriorate the allograft function in patients subject to optimal treatments with tacrolimus, as published by Staatz (2). On the contrary, maintaining full MPA doses allows for a safe reduction in CNI exposure without increasing acute rejection episode rates (2).

The purpose of this analysis is to warn the transplant community that an unwise and unconscious decision to reduce MPA doses alongside CNI exposure with the intention of improving GFR could result, in fact, in an undesired AMR.

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