P162

Impact of Tacrolimus Intra-Individual Variability and CYP3A5 Genetic Polymorphism on Acute Rejection in Kidney Transplantation

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Background: Wide variation in tacrolimus levels and low tacrolimus exposure were reported to be associated with poor renal graft outcomes in non-Asians. The CYP3A5 polymorphism is a representative genetic factor that might affect this association together with environmental factors. We investigated whether tacrolimus variability or the mean tacrolimus trough level can influence kidney allograft outcomes in Asians, and whether the CYP3A5 polymorphism (rs776746) can affect this relationship.

Methods: Renal transplant patients between January 1, 1996 and January 31, 2010 were retrospectively analyzed. The tacrolimus intra-individual variability (IIV) and the mean tacrolimus trough level were calculated from the tacrolimus levels between 6 and 12 months after transplantation.

Results: A total of 249 renal transplant patients were enrolled. The patients with higher tacrolimus IIV had shorter rejection-free survival (P= 0.002). However, there was no difference in rejection-free survival between CYP3A5 expressers and non-expressers. The tacrolimus IIV was not associated with the CYP3A5 polymorphism. High IIV of tacrolimus was an independent risk factor of biopsy-proven acute rejection after adjusting for mean tacrolimus concentration, HLA mismatch, induction therapy, donor type, and CYP3A5 polymorphism. Interestingly, the impact of tacrolimus IIV on acute rejection was significant in CYP3A5 expressers, whereas it was not in CYP3A5 non-expressers.

Conclusion: The intra-individual variability of tacrolimus trough concentrations had a significant impact on rejection-free survival. The effect was influenced by CYP3A5 polymorphism, although the tacrolimus variability itself was not determined by the CYP3A5 polymorphism.

Key Words: 타크로리무스, 개체 내 다양성, 싸이토크롬P3A5, 신이식
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