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The Optimal Tacrolimus Trough Level After Liver Transplantation

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Lecture : Introduction Optimal immunosuppressant drug therapy is essential for maintaining a viable organ allograft. Immunosuppressive agents are critical dose drugs exhibiting the desired therapeutic effect with an acceptable tolerability within a narrow range of blood concentrations. Furthermore, they exhibit a high degree of between-individual pharmacokinetic and pharmacodynamic variability, which may result in an increased risk of therapeutic failure if these agents are used at uniform doses in all patients. The correlation between blood drug concentrations and clinical outcomes is an important factor supporting the use of therapeutic drug monitoring (TDM). Individualizing a patient's drug therapy to obtain the ideal balance between therapeutic efficacy and the occurrence of adverse events is the primary goal of the clinician. Each patient must be considered individually. They will respond to a drug due to differences in age, body weight, fat/lean tissue content, enzymatic activities, kidney or liver function, and concomitant therapies. Pharmacokinetic, pharmacodynamic, and more recently pharmacogenetic approaches aid physicians to individualize long-term therapies. Target ranges for efficacy Initial tacrolimus (TAC) target ranges were relatively broad, ranging between 5 and 40 ng/mL, subsequently, lower trough concentrations were adopted, varying between 10 and 20 ng/mL. Interestingly, despite these high target ranges, acute rejection rates ranged between 41%and 45% of patients in these early trials, which can possibly be explained by the limited practical experience with the drug and the concomitant use of azathioprine instead of MMF and/or the lack of induction therapy. The first consensus conference on TAC optimization concluded that TAC whole blood concentrations were targeted between 5 and 20 ng/mL for all transplant populations. The gain in clinical experience together with the introduction of MMF and induction therapies [IL-2 monoclonal antibodies (mAb): daclizumab and basiliximab] led to a dramatic reduction of rejection rates to between 8% and 20%, simultaneously with a reduction in the target whole blood TAC concentrations to 10–15 ng/mL or even 8–12 ng/mL and with some improvement in the identification of surrogate end points like allograft function, side effects, adverse events, and quality of life. Careful interpretation of recent clinical data, albeit without performing a formal systematic review, allows us to roughly position current effective target trough TAC concentrations between 5 and 10 ng/mL, at least in the first year after transplantation provided that TAC is incorporated in an immunosuppressant regime with mycophenolate, corticosteroids, and anti-IL-2 mAb induction. Adverse events Although it is obvious

that increasing TAC concentrations may lead to an increase in drug-related adverse effects, it is difficult to establish a clear cutoff due to a substantial overlap between concentration ranges of increased efficacy and the appearance of adverse effects. Patients with low TAC exposure displayed a better 1-year graft function, probably both as a result of reduced cumulative alloimmune injury and less drug-related nephrotoxicity. The combination of TAC, MMF, and corticosteroids still retained its characteristic toxicity, resulting in more diarrhea (27.4%) and new-onset diabetes mellitus after transplantation (NODAT) (10.6%). Moreover, drug-related toxicity remains often difficult to quantify due to differences in study design, definition of toxicity, diagnosis and registration of adverse events, differences in non-immunosuppressive concomitant medication, length of follow-up, and study populations. Conclusion TDM of TAC remains a major support to patient management, to assess compliance, to prevent adverse events, and in the detection of drug interactions or unexpected pharmacogenetic influences. Trough concentration monitoring, although not the ideal marker, is still widely used as a guide to individualizing TAC dose requirements. The relationship between high trough concentrations and toxicity has been demonstrated in various studies References 1. Wallemacq P. et al. Opportunities to Optimize Tacrolimus Therapy in Solid Organ Transplantation: Report of the European Consensus Conference. Ther Drug Monit 2009;31:139-152. 2. Lancia P. et al. Choosing the Right Dose of Tacrolimus. Arch Dis Child 2015;100:406-413. 3. Scalea JR. et al. Tacrolimus for the prevention and treatment of rejection of solid Organ Transplants. Exp Rev Clin Immunol 2016;12:333-342. 4. Londono MC. et al. Immunosuppression minimization vs. complete drug withdrawal in liver transplantation. J Hepatol 2013;59:872-879