Immunologic Monitoring to Personalize Immunosuppression After Liver Transplant

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KEYWORDS

• Liver transplantation • Immunosuppression • Biomarker monitoring
• Personalization • Pharmacogenetics

KEY POINTS

- Immunosuppressive drugs exhibit a wide array of side effects, and current methods of immunosuppressive monitoring are unable to adequately account for individual variation to these drugs.
- Ongoing research in biomarker monitoring has produced promising results in early diagnosis of graft damage or immune response.
- In particular, microRNA biomarkers and regulatory T lymphocytes are leading candidates as biomarkers of organ damage and immune response, respectively.
- Introduction and improvement of genetic sequencing techniques has allowed more powerful, statistically significant results in the identification of drug-specific and nonspecific genes.

INTRODUCTION

In the past few decades, advances in pharmacologic immunosuppressive agents have led to large improvements in overall outcomes of liver transplants. However, there are still significant issues with risks for long-term drug adverse events for transplant recipients. Current immunosuppressive drug regimens are one-size-fits-all, with many recipients being either oversuppressed (leading to drug toxicity) or undersuppressed (leading to adverse immune reaction): preliminary general findings from clinical trials (iWITH and A-WISH) indicate that more than half of

Disclosure Statement: The authors have nothing to disclose.

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Gastroenterol Clin N Am 47 (2018) 281–296
https://doi.org/10.1016/j.gtc.2018.01.003
gastro.theclinics.com

individuals can tolerate a 50% reduction in standard immunosuppressive therapy and more than one-third of individuals can tolerate a 75% reduction.[1] Because much of the risk in transplantation stems from the difficulty of predicting individual patient response to drug regimens, the transplant community continues to seek out methods of personalized dosing to balance adequate immune suppression while reducing harmful side effects of pharmacotherapy. This article presents a brief background into the current repertoire of immunosuppressive management in liver transplantation before focusing on the developing efforts for personalized immunosuppression in liver transplantation via biomarkers.

CURRENT IMMUNOSUPPRESSION MANAGEMENT

Contemporary Monitoring Methods in Liver Transplantation

Many immunosuppressive drugs exhibit a wide variability in pharmacokinetic behavior combined with a narrow therapeutic index, making it challenging for physicians to administer the optimal dosages of immunosuppressive agents during and after transplant. Therefore, to ensure best patient outcomes, close therapeutic drug monitoring becomes essential to minimize adverse effects of immunosuppressive drug regimens while avoiding chronic or acute organ rejection. Although calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors are closely monitored because of their narrow therapeutic range and potential for adverse pleiotropic effects, corticosteroids and costimulatory blockers (belatacept) do not usually require therapeutic drug monitoring.[2] For nearly all immunosuppressive drugs, specimen collection occurs at the trough level or predose level, immediately before the next round of drug administration. Known as C0 trough monitoring, this approach serves to standardize measurements and results (**Fig. 1**). The 1 exception is cyclosporine A (CsA) monitoring, which occurs 2 hours postdosing, also known as C2 monitoring.[3] Most of these techniques require pretreatment of whole blood to determine the relevant drug concentrations.[2] Blood plasma is usually not sufficient for analysis, per se, because most immunosuppressants are distributed unevenly throughout blood, leading to differences in drug concentration within the various blood components. Mycophenolic acid (MPA) measurements remain an exception, because nearly all MPA is found in plasma, so therapeutic drug monitoring for MPA can be conducted with only blood serum or plasma.[4]

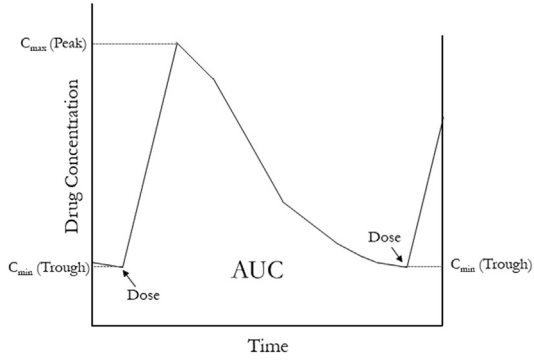

Fig. 1. Drug levels over dosing interval. Drug concentrations decrease to minimum trough level (C0) before increasing to peak concentration C_{max}. The area under the concentration-time curve (AUC) gives total drug exposure in the timespan.