A Closer Look at the Immunology/Transplantation PRN

Overview of the PRN

The ACCP Immunology/Transplantation (IMTR) PRN was founded in 1993 to foster collaboration, education, and communication between immunology and transplant practitioners across a variety of health care settings. With the rapid establishment and growth of transplant centers across the United States, the increasing need and role for transplant pharmacists caught the attention of national policy-makers. As a result, 2004 amendments to the United Network for Organ Sharing bylaws included transplant pharmacists as an integral member of the transplant multidisciplinary team. Not long after these amendments, the Centers for Medicare & Medicaid Services Conditions of Participation for organ transplant centers required that every transplant program have a designated, qualified expert in transplant pharmacology. Institution of these policies allowed an initial handful of transplant pharmacists to blossom into greater than 500 transplant pharmacists committed to patient care, research, and trainee education, of which the PRN is currently composed.

The IMTR PRN's mission is to improve the health of tissue, cellular, and solid organ transplant donors and recipients and patients with immunologic disorders by fostering practice innovation, supporting outcomes and translational research, and providing high-quality education to patients and practitioners. The PRN serves as the society-based organization for modeling and advancing immunology and transplant pharmacy by promoting excellence in practice, research, and education through collaboration, innovation, and leadership in an effort to optimize patient outcomes and quality of life. This mission and vision is accomplished through providing regular educational programs, funding grants for pharmacist-driven research, and serving as an open forum of communication among the PRN's members to share policies, protocols, and clinical experiences.

PRN Leadership:

Chair:
Barrett Crowther, Pharm.D., FAST, BCPS
Chair-Elect:
James Fleming, Pharm.D., BCPS
Immediate Past Chair:
Chris Ensor, Pharm.D., BCPS
Secretary/Treasurer:
Carissa Garza, Pharm.D., BCPS
Trainee Officer:
John Lyons, Pharm.D.

Membership Overview:

Total Members: 530
Resident Members: 39
Fellow Members: 9
Student Members: 161

Opportunities and Resources for Student, Resident, and Fellow Members

The IMTR PRN's current success and continued growth are largely the result of its active student, resident, and fellow members. In addition to providing an avenue for practitioners to share clinical expertise, research endeavors, and career opportunities through the e-mail list, the PRN provides a large network of committees in which residents and students are encouraged to become involved and serve leadership roles, such as the Nominations, Research, Historian/Communications, and Programming committees and the New Practitioner Council. Currently, every committee has at least one, if not several, active resident and fellow members, as well as one student liaison. New practitioners and trainees can connect with experienced PRN members through a newly established mentorship program, in addition to the events and new initiatives that are continually developed by the PRN New Practitioner Council. The PRN also funds an annual IMTR Resident/Fellow Travel Award to cover travel expenses for a select few resident/fellow members presenting exceptional transplant/immunology-related research at the ACCP Annual Meeting.

For students and residents curious about the wonderful opportunities that a career in transplantation affords, the New Practitioner Council hosts the annual "Role of the Transplant Pharmacist" webinar in conjunction with the American College of Clinical Pharmacy Student Chapter. This webinar serves as a forum to present all the unique roles and practice settings held by the IMTR PRN's current members, as well as answers any questions that students and residents may have.

Looking to the Future

As the role of clinical pharmacists continues to evolve and patient needs become more complex, therapeutic options in immunology will require expertise beyond solid organ or bone marrow transplantation. A long-term goal of the IMTR PRN is to expand the membership of clinical pharmacists in non-transplant immunology specialties such as rheumatology and autoimmunity. In addition to welcoming non-transplant immunology specialists, the PRN is committed to collaborating with other pharmacy specialties in practice and research.

Clinical Controversy: Tacrolimus—Are All Formulations Created Equal?

Tacrolimus, the calcineurin inhibitor first FDA approved in 1994 under the brand name Prograf, has become the gold standard backbone for immunosuppressive regimens in the United States across the field of organ transplantation.[1] Prograf, an immediate-release formulation of tacrolimus, is typically dosed every 12 hours and requires therapeutic drug monitoring—specifically, with serum trough concentrations. Since the release and incorporation of Prograf into institution protocols across the United States, two novel extended-release formulations have been released: Astagraf and Envarsus XR.[2,3] In addition, the 2008 expiration of the tacrolimus patent has given rise to several generic manufacturers. Although the parent drug, tacrolimus, is constant across these many formulations, each formulation offers a unique pharmacokinetic (PK) and dosing profile, allowing for a patient-centered approach to tacrolimus-based immunosuppression. Despite the seemingly many options, patients must be monitored carefully to prevent confusion and potential drug-related errors across the continuum of care.

A randomized, prospective, open-label, multicenter, crossover PK study by Alloway et al. evaluated the PK differences between brand and generic tacrolimus formulations in stable renal transplant recipients.[4] After a 14-day run-in period, 71 patients were randomized to either remain on the reference Prograf formulation or receive generic tacrolimus (Sandoz). Patients were continued on their respective tacrolimus formulations for an additional 14 days and then crossed over to the alternative formulation. No significant differences in $AUC_{0\text{-}12hr}$, C_{max}, or C_0 were found between groups, and no clinical rejection episodes or graft losses occurred during the study period. The 90% CI values for the ratios of geometric means of $AUC_{0\text{-}12hr}$ and C_{max} were 97%–108% and 101%–118%, well within the 80%–125% range to meet the FDA criteria for bioequivalence. This was the first randomized PK study to support the bioequivalence of generic tacrolimus and brand Prograf in a cohort of renal transplant recipients.[4] One important caveat of this study is that it addresses only a single generic manufacturer's comparison with reference tacrolimus (Prograf). Although all generic manufacturers of tacrolimus were required to demonstrate $AUC_{0\text{-}12hr}$ and C_{max} within the 80%–125% range for FDA criteria for bioequivalence, no study has directly compared different generic manufacturers.

Astagraf XL, an extended-release formulation of tacrolimus, uses a matrix of three excipients, which form a polymer gel layer around tacrolimus.[2] This layer decreases the drug's penetration, extending drug delivery along the gastrointestinal (GI) tract. Astagraf XL was FDA approved in 2013 for the prophylaxis of organ rejection in kidney transplant recipients. When converting from immediate-release tacrolimus, the manufacturer recommends a 1:1 conversion between the products, although they are not considered bioequivalent.[2]

Envarsus XR, a recently released extended-release tacrolimus formulation, uses MeltDose technology, in which the particle size of tacrolimus is reduced to form a "solid solution," which is subsequently sprayed onto a carrier molecule and pressed into an extended-release tablet.[3] This novel formulation allows for the enhanced bioavailability of tacrolimus as well as its sustained release across all portions of the GI tract. Envarsus XR was FDA approved in 2015 for the prophylaxis of organ rejection in kidney transplant recipients, but it is only approved for conversion from a stable dose of immediate-release tacrolimus at 80% of the total daily dose of immediate-release tacrolimus.[3]

A recently published randomized, open-label, crossover PK study, ASTCOFF, is the only study to date to compare all immediate- and extended-release tacrolimus formulations.[5] Thirty-one patients were randomized to two separate drug sequences, receiving each tacrolimus formulation (Prograf, Astagraf XL, and Envarsus XR) for 1 week. At the end of each week, steady-state 24-hour PK profiles were collected and compared, as described in Table 1. Prograf and Astagraf XL were not significantly different in $AUC_{0\text{-}24hr}$ and C_{max}, but Astagraf XL had a significantly lower C_{min}. Envarsus XR had a significantly higher $AUC_{0\text{-}24hr}$, lower intraday peak-to-trough fluctuation, and longer T_{max}. Envarsus XR also had a significantly higher bioavailability (around 50%). Study results show that each formulation has its own unique pharmacokinetic profile and that the three formulations are not interchangeable. To date, no randomized controlled trial has successfully evaluated differences in adherence patterns with once- versus twice-daily tacrolimus formulations.[5]

Table 1. Summary of Observed PK Parameters (n=30)

Observed PK Parameter	Observed Results			Comparisons		
	LCPT	ER-Tac	IR-Tac	LCPT vs. IR (%)	ER vs. IR (%)	LCPT vs. ER (%)
Mean total daily dose (mg ± SD)	4.9 ± 2.3	6.1 ± 2.9	6.1 ± 2.9	—	—	—
$AUC_{0\text{-}24hr}$ (hr × ng/mL ± SD)	213.4 ± 83.1	165.0 ± 50.0	176.5 ± 50.8	117.0[a] (107.9, 127.0)	93.1 (85.8, 101)	125.7[a] (114.1, 138.5)
C_{max} (ng/mL ± SD)	13.9 ± 5.3	13.2 ± 4.4	14.5 ± 5.5	94.7 (85.8, 104.4)	91.8 (83.2, 101.3)	103.1 (92.4, 115.0)
C_{min} (ng/mL ± SD)	6.8 ± 2.9	5.1 ± 1.8	6.1 ± 1.7	107.0 (97.6, 117.2)	83.0[a] (75.7, 90.9)	128.9[a] (117.4, 141.6)
T_{max} (hr)	5.9 (1.5, 14.0)	1.9 (0.9, 5.9)	1.5 (0.9, 20.0)	3.0[a] (1.6, 4.4)	0.1 (–0.4, 0.5)	3.0[a] (1.9, 4.0)

[a]$p<0.05$.

ER = extended release; IR = immediate release; LCPT = a novel once-daily formulation of tacrolimus; Tac = tacrolimus.

Adapted from: Tremblay S, Nigro V, Weinberg J, et al. A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open-label, prospective, randomized, two-arm, three-period crossover study. Am J Transplant 2017;17:432-42.

Development of novel tacrolimus formulations has provided clinicians with both once- and twice-daily tacrolimus formulations, each with its own unique PK profile. Although the tacrolimus generic formulations are considered bioequivalent to the reference tacrolimus, Prograf, products may not be readily interchangeable without appropriate monitoring. In addition, the decision to convert a

patient to a once-daily extended-release tacrolimus formulation from the traditional immediate-release twice-daily formulation requires a concerted effort among transplant providers to ensure appropriate therapeutic drug monitoring without significant interruption in a patient's immunosuppression.

References

1. Prograf [package insert]. Northbrook, IL: Astellas Pharma US, 2013.
2. Astagraf XL [package insert]. Northbrook, IL: Astellas Pharma US, 2014.
3. Envarsus XR [package insert]. Edison, NJ: Veloxis, 2016.
4. Alloway RR, Sadaka B, Trofe-Clark J, et al. A randomized pharmacokinetic study of generic tacrolimus versus reference tacrolimus in kidney transplant recipients. Am J Transplant 2012;12:2825-31.
5. Tremblay S, Nigro V, Weinberg J, et al. A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open-label, prospective, randomized, two-arm, three-period crossover study. Am J Transplant 2017;17:432-42.