Variation in Comedication Use According to Kidney Transplant Immunosuppressive Regimens: Application of Integrated Registry and Pharmacy Claims Data

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ABSTRACT

Background. Modern immunosuppression therapies (ISx) have many side effects, and transplant recipients must take an array of "comedications" to help mitigate complications. Comedication use patterns are not well described in large, representative samples because of lack of data.

Methods. We integrated national U.S. transplant registry data with pharmacy records (2005–2010) from a large pharmaceutical claims clearinghouse to examine treatments for anemia, metabolic disorders, and infections in relation to ISx regimens in months 6–12 post-transplantation (N = 22,453). Associations of ISx with comedication use (adjusted odds ratio [aOR]) were quantified with multivariate logistic regression including adjustment for recipient, donor, and transplant factors.

Results. Compared to a reference regimen of tacrolimus, mycophenolic acid, and prednisone, sirolimus-based ISx was associated with significantly more common use of erythropoiesis-stimulating agents (aOR 2.52, 95% confidence interval [CI] 2.06–3.09), iron (aOR 2.26, 95% CI 1.92–2.65), statins (aOR 1.47, 95% CI 1.33–1.63), fibrates (aOR 2.35, 95% CI 1.90–2.90), and phosphorous binders (aOR 2.85, 95% CI 1.80–4.50). Patterns were similar after adjustment for first-year estimated glomerular filtration rate, except the association with phosphorous binders was no longer significant. Cyclosporine-based ISx was associated with more common erythropoiesis-stimulating agent use, including after estimated glomerular filtration rate adjustment (aOR 1.61, 95% CI 1.24–2.10). Compared to those who were being administered triple ISx, recipients receiving tacrolimus-based dual and monotherapies had lower use of statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs), and antibacterial agents. Recipients of steroid-free ISx were less commonly treated for post-transplantation diabetes.

Conclusions. Alternate ISx regimens are associated with varying treatment requirements for hematologic, metabolic. and infectious complications. Comedication use should be considered in the cost-effectiveness and individualization of ISx regimens.

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MODERN transplant immunosuppression (ISx) is a "double-edged" sword. Although potent immunosuppressive therapies have substantially reduced the risk of acute rejection in the last decade [1], ISx medications are associated with multiple side effects including increased risks of metabolic disorders, anemia, and infections. Thus, transplant recipients must receive an array of "comedications" to help mitigate side effects, reduce complications, and promote long-term health. Comedication use patterns are not well described in large, representative samples because of the lack of available data. Prospective cohort studies [2] and center-based data aggregation efforts such as the Predicting Outcomes in Renal Transplantation (PORT) project, a multicenter collaborative of non-immunosuppressive medication use in the kidney transplantation population [3], can provide rich clinical information on post-transplantation medication use and comorbidities, but such studies are time-intensive, resource-intensive, and expensive to conduct. To advance understanding of comedication use in relation to ISx regimens in a large national sample we integrated U.S. transplantation registry data with pharmacy fill records from a large pharmaceutical claims clearinghouse. Our primary goals were to identify treatments for anemia, metabolic disorders, and infections, important therapies not tracked in the national registry, and to examine use of these comedications according to ISx regimen during months 6–12 post-transplantation.

METHODS

This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the OPTN, and has been described elsewhere. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN contractor. Study data were constructed by linking OPTN records for kidney transplant recipients with pharmacy fill records from a large U.S. pharmaceutical claims data (PCD) clearinghouse that captures prescription drug fill records, including those reimbursed by private payers, public payers, and self-paid fills. The PCD comprises the National Council for Prescription Drug Program (NCPDP) 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies, and prescription benefit managers for approximately 60% of U.S. retail pharmacy transactions. After Institutional Review Board and OPTN/HRSA approvals, PCD records (2005 to 2010) were linked with OPTN records for kidney transplant recipients using an encrypted transformation of last name, first name, date of birth, and ZIP code. Analyses were performed using Health Information Portability and Accountability Act (HIPAA)–compliant, limited datasets from which all direct identifiers were removed. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, paragraph 46.116).

Eligible renal allograft recipients had OPTN records of receiving a kidney transplant and pharmacy claims in the PCD (2005 to 2010 records) during months 6–12 post-transplantation. ISx regimens during months 6–12 after transplantation were classified based on ISx fills as: 1) tacrolimus (Tac), mycophenolic acid (MPA, which included mycophenolate mofetil (MMF) and mycophenolate sodium), and prednisone; 2) Tac and MPA; 3) Tac alone or with prednisone; 4) cyclosporine (CsA)–based; 5) sirolimus-based; or 6) other regimens. Triple ISx with Tac, MPA and prednisone was considered the reference regimen. We identified comedication use from pharmacy fills in the same period. Erythropoiesis-stimulating agents (ESAs) and iron supplements were examined as anemia treatments. Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) and fibrates were studied as major lipid-lowering therapies. Diabetes therapies (oral agents and insulin) were examined among patients without pretransplantation diabetes as a measure of post-transplantation diabetes mellitus (PTDM). We also extracted angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers (ACEi/ARBs), which may be indicated for hypertension and/or proteinuria. Finally, we investigated antibacterial treatments, excluding agents commonly used for pneumocystis prophylaxis (trimethoprim-sulfamethoxazole, pentamidine, dapsone, atovaquone) and use of phosphate binders. Associations of ISx with comedication use (adjusted odds ratio [aOR]) were quantified by multivariate logistic regression including adjustment for baseline recipient, donor, and transplant factors captured in the OPTN registry (recipient age, sex, race, body mass index, cause of renal failure, diabetes, hypertension, coronary artery disease/angina, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral vascular disease, education, employment status, previous transplantation, panel reactive antibody, cytomegalovirus serostatus, human leukocyte antigen mismatch level, and donor type and ethnicity). Secondary analyses included adjustment for estimated glomerular filtration rate (eGFR) based on 1-year serum creatinine levels reported to the OPTN.

RESULTS

The study sample comprised 22,453 kidney transplant recipients for whom ISx regimens in months 6–12 post-transplantation were as follows: Tac + MPA + prednisone (33.8%); Tac + MPA without steroids (25.8%); Tac alone or with prednisone (11.3%); CsA-based (7.8%); sirolimus-based (9.9%); and others (11.6%). The majority (82%) of patients receiving CsA also received MPA. Compared to the reference regimen of Tac + MPA + prednisone, sirolimus-based ISx was associated with significantly more common use of ESAs (aOR 2.52, 95% confidence interval [CI] 2.06–3.09), iron (aOR 2.26, 95% CI 1.92–2.65), statins (aOR 1.47, 95% CI 1.33–1.63), fibrates (aOR 2.35, 95% CI 1.90–2.90), and phosphorous binders (aOR 2.85, 95% CI 1.80–4.50) (Fig 1). Patterns were similar after eGFR adjustment, except that the association with phosphorous binder use was no longer significant. CsA-based ISx was associated with more common use of ESAs and iron treatments in primary analyses, and the association with ESA use persisted after adjustment for eGFR (aOR 1.61, 95% CI 1.24–2.10). Compared to those receiving the reference triple ISx regimen, patients receiving Tac + prednisone or Tac monotherapy had lower use of statins (aOR 0.51, 95% CI 0.46–0.56), ACEi/ARBs (aOR 0.66, 95% CI 0.59–0.74), and antibacterial agents (aOR 0.89,