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VARIATION IN CO-MEDICATION 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 “co-medications” to help mitigate complications. Co-medication use patterns are not well described in large, representative samples due to 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 according to ISx regimen in months 6–12 post-transplant (N=22,453). Associations of ISx with co-medication 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 ESAs (aOR 2.52, 95% 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

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Disclosures

The authors have no conflicts of interest related to this work.

were similar after adjustment for first-year estimated glomerular filtration rate (eGFR), except the association with phosphorous binders was no longer significant. Cyclosporine-based ISx was associated with more common ESA use, including after eGFR adjustment (aOR 1.61, 95%CI 1.24-2.10). Compared to those taking triple ISx, recipients taking tacrolimus-based dual and mono-therapies had lower use of statins, ACEi/ARBs, and anti-bacterial agents. Recipients of steroid-free ISx were less commonly treated for post-transplant diabetes.

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

Introduction

Modern transplant immunosuppression (ISx) is a “double-edged” sword. While 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 take an array of “co-medications” to help mitigate side effects, reduce complications, and promote long-term health. Co-medication use patterns are not well described in large, representative samples due to 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 multi-center collaborative of non-immunosuppressive medication use in the kidney transplant population ³, can provide rich clinical information on post-transplant medication use and comorbidities, but such studies are time-intensive, resource-intensive and expensive to conduct. To advance understanding of co-medication use in relation to ISx regimen in a large, national sample, we integrated U.S. transplant 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 co-medications according to ISx regimen during months 6-12 post-transplant.

Methods

This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the OPTN, and has been described elsewhere (43). 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 billing claims 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 of 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. Due to the large sample size, the anonymity of the patients studied, and the non-intrusive 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 to 12 post-transplantation. ISx regimens in months 6-12 after transplant were classified based on ISx fills as: (1) tacrolimus (Tac), mycophenolate acid (MPA, mycophenolic mofetil or mycophenolate sodium) and prednisone (**Reference Regimen**), (2) Tac and MPA, (3) Tac alone or with prednisone, (4) cyclosporine (CsA)-based, (5) sirolimus-based, or (6) other regimens. We identified co-medication use from pharmacy fills in the same period. Erythropoiesis-stimulating agents (ESAs) and iron supplements were examined as anemia treatments. HMG-CoA reductase inhibitors (statins) and fibrates were studied as major lipid-lowering therapies. Diabetes therapies (oral and insulin) were examined among patients without pre-transplant diabetes as a measure of post-transplant diabetes mellitus (PTDM). We also extracted ACE-inhibitors/Angiotensin-II Receptor Blockers (ACEs/ARBs), which may be indicated for hypertension and/or proteinuria. Finally, we investigated anti-bacterial treatments, excluding agents commonly used for pneumocystis prophylaxis (trimethoprim-sulfamethoxazole, pentamidine, dapsone, atovaquone) and use of phosphate binders. Associations of ISx with co-medication 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 analysis included adjustment for estimated glomerular filtration rate (eGFR) based on one-year serum creatinine levels reported to the OPTN.

Results

The study sample comprised 22,453 kidney transplant recipients, among whom ISx regimens in months 6-12 post-transplant comprised: 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 taking CsA also received MMF. Compared to a reference regimen of Tac+MPA+prednisone, sirolimus-based ISx was associated with significantly more common use of ESAs (aOR 2.52, 95% 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) (**Figure 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 analysis, and the

association with ESA use persisted after adjustment for eGFR (aOR 1.61, 95%CI 1.24-2.10). Compared to those taking the reference triple ISx regimen, patients receiving Tac +prednisone or Tac mono-therapy 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 anti-bacterial agents (aOR 0.89, 95%CI 0.80-0.99). Similar patterns of lower use of statins (aOR 0.72, 95% CI 0.67-0.78), ACEi/ARBs (aOR 0.77, 95% CI 0.70-0.83) and antibacterial agents (aOR 0.74, 95%CI 0.68-0.80) were also seen in the Tac+MPA group. Recipients taking steroid-free ISx (Tac+MPA) (aOR 0.57, 95%CI 0.49-0.66) and CsA-based therapy (aOR 0.76, 95%CI 0.62-0.94) were less commonly treated for PTDM than those taking the reference ISx regimen.

Discussion

Transplant recipients require numerous co-medications to manage complications related to ISx and underlying comorbidities. However, co-medication utilization patterns are not well described in large, representative samples due to lack of data. In the current study, we examined a novel linkage of national transplant registry and pharmacy fill records to quantify co-medication use in relation to ISx regimen over months 6-12 post-transplant. Among the findings, sirolimus- and CsA-based regimens were associated with increased use of anemia treatments. Specifically, compared to the reference Tac+MPA+prednisone regimen, sirolimus-based ISx was associated with the twice the likelihood of ESAs and iron use. This observation is consistent with the high prevalence of anemia commonly seen among patients managed with sirolimus-based ISx, attributable to multiple factors including reduced erythropoietin production and increased inflammation⁴. Notably, CsA-based ISx was associated with an 80% increase in the likelihood of ESA use and 20% higher likelihood of iron therapy; while adjustment for eGFR attenuated the effects, a 61% higher likelihood of ESA use among CsA-treated patients persisted after eGFR adjustment. This observation runs counter to some prior studies demonstrating associations of Tac with higher likelihood of post-transplant anemia⁵. In the current study, the majority of patients on CsA-based regimen received MPA, but we did not have access to calcineurin inhibitor or MPA levels. The impact of MPA on anemia is dose-dependent⁶, and it is possible that intensity of MPA exposure differed across the treatment groups in our study.

Historically, single- and multi-center reports have estimated that, by one year post-transplant, 80 to 90% of adult kidney transplant recipients had total cholesterol levels >200 mg/dL, and >90% had LDL levels >100 mg/dL^{7,8}, but a more recent multicenter prospective cohort study reported LDL levels >100 mg/dL among 45% of patients at six months posttransplant, a pattern that likely reflect lower target levels of modern ISx agents as well as concomitant statin treatment in 41%². While glucocorticoids, calcineurin inhibitors (CsA typically more than Tac) and mTOR inhibitors contribute to the high prevalence of post-transplant dyslipidemia, the effects of mTOR inhibitors are distinct in predominantly causing hypertriglyceridemia⁹. We observed that compared to patients taking the reference ISx regimen, those receiving sirolimus-based ISx had 2.3-times the use of fibrates and 50% higher statin use. In contrast, consistent with expected associations with less dyslipidemia risk, ISx minimization in the form of Tac+ MMF, and Tac alone or with prednisone, was associated with 30%-50% lower adjusted requirements for statins and fibrates.

PTDM has been associated with calcineurin inhibitors (Tac more than CsA), mTOR inhibitors and steroids¹⁰. Consistently, we identified 20-25 % lower use diabetes treatments among patients managed with ISx minimization in the form of Tac+ MMF, and Tac alone or with prednisone compared to the reference regimen. Other associations between ISx regimen and co-medication treatment patterns were observed. Sirolimus-based ISx and Tac monotherapy/Tac+ prednisone were associated with more frequent phosphate binder use compared to the reference ISx regimen in primary analyses. However, these associations were not significant after adjustment for eGFR, supporting mediation by allograft function. Independent of eGFR, ACEi/ARB use was approximately 23% lower with Tac+MPA compared to the reference ISx regimen, likely reflecting less hypertension in the absence of prednisone (lower mineralocorticoid effect). Sirolimus may promote proteinuria, and was associated with similar ACEi/ARB use as the reference triple ISx regimen. Finally, antibacterial treatments were approximately 10% to 25% less common among those managed with Tac-based mono or dual therapies, consistent with less infection risk from an overall reduction in immunosuppression.

The current study is limited by its retrospective cross-sectional design, which can determine associations but not prove causation. The available data do not include detailed clinical information that may explain contraindications to the use of particular study medications. We did not have access to lab data such as hemoglobin, lipid or ISx drug levels. However, medication fills serve as surrogate measures of clinical conditions in this design; adjustment for mediating factors such lab values would obscure the associations of interest. Co-medications were considered as binary outcomes that do not discriminate the intensity of treatments. We also lacked information on variables such as socioeconomic status that may have affected treatment decisions. Further, while electronic pharmacy claims and fill records have been shown to be highly accurate records of physician prescribing^{11,12}, claims data do not capture use of over-the-counter medications.

In conclusion, examination of integrated transplant registry and pharmacy fill records demonstrates that alternate ISx regimens are associated with varying degrees of treatments for hematologic, metabolic and infectious complications. Integrated pharmacy claims can provide measures of healthcare resource utilization and serve as a surrogate measures of comorbidities not tracked in the national transplant registry. Co-medication use should be considered in studies of the cost-effectiveness and individualization of ISx regimens.

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Research Highlights

We examined a novel linkage of national U.S. transplant registry and pharmacy fill records to quantify use of “co-medications” to manage comorbidities in relation to immunosuppression regimens.

Alternate immunosuppression regimens are associated with varying degrees of treatments for hematologic, metabolic and infectious complications.

Integrated pharmacy claims can provide measures of healthcare resource utilization and serve as a surrogate measures of comorbidities not tracked in the national transplant registry.

Co-medication use should be considered in studies of the cost-effectiveness and individualization of immunosuppression regimens.

Figure 1.
Co-medication Use by Immunosuppression Regimen, 6-12 months post-transplant.