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Outcomes Following Macrolide Use in Kidney Transplant Recipients

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Abstract

Background: Calcineurin inhibitors (CNI; cyclosporine, tacrolimus) are critical for kidney transplant immunosuppression, but have multiple potential drug interactions, such as with macrolide antibiotics. Macrolide antibiotics (clarithromycin, erythromycin, and azithromycin) are often used to treat atypical infections. Clarithromycin and erythromycin inhibit CNI metabolism and increase the risk of CNI nephrotoxicity, while azithromycin does not.

Objective: To determine the frequency of CNI-macrolide co-prescriptions, the proportion who receive post-prescription monitoring, and the risk of adverse drug events in kidney transplant recipients.

Design: Retrospective cohort study.

Setting: We used linked health care databases in Alberta, Canada.

Patients: We included 293 adult kidney transplant recipients from 2008-2015 who were co-prescribed a CNI and macrolide.

Measurements: The primary outcome was a composite of all-cause hospitalization, acute kidney injury (creatinine increase $\geq$0.3 mg/dL or 1.5 times baseline), or death within 30 days of the macrolide prescription.

Methods: We identified CNI-macrolide co-prescriptions and compared outcomes in those who received clarithromycin/erythromycin versus azithromycin. We used a linear mixed-effects model to examine the mean change in serum creatinine and estimated glomerular filtration rate (eGFR).

Results: Of the 293 recipients who were co-prescribed a CNI and a macrolide, 38% (n = 112) were prescribed clarithromycin/erythromycin while 62% (n = 181) were prescribed azithromycin. Compared with azithromycin users, clarithromycin/erythromycin users were less likely to have outpatient serum creatinine monitoring post-prescription (56% vs 69%, $P = .03$). There was no significant difference in the primary outcome between the 2 groups (17% vs 11%, $P = .11$); however, the risk of all-cause hospitalization was higher in the clarithromycin/erythromycin group (10% vs 3%, $P = .02$). The mean decrement in eGFR was significantly greater in the clarithromycin/erythromycin versus azithromycin group (−5.4 vs −1.9 mL/min/1.73 m^2, $P < .05$).

Limitations: We did not have CNI levels to correlate with the timing of CNI-macrolide co-prescriptions. We also did not have information regarding the indications for macrolide prescriptions.

Conclusion: Clarithromycin and erythromycin were frequently co-prescribed in kidney transplant recipients on CNIs despite known drug interactions. Clarithromycin/erythromycin use was associated with a higher risk of hospitalization compared with azithromycin users. Safer prescribing practices in kidney transplant recipients are warranted.

Abrégé

Contexte: Les inhibiteurs de la calcineurine (CNI : cyclosporine, tacrolimus) sont essentiels à l'immunosuppression suivant une transplantation rénale. Ils présentent toutefois de nombreux risques d'interactions médicamenteuses avec les antibiotiques macrolides (clarithromycine, érythromycine et azithromycine) employés couramment pour traiter les infections atypiques. La clarithromycine et l'érythromycine inhibent le métabolisme des CNI et augmentent leurs risques de néphrotoxicité, ce qui n'est pas le cas de l'azithromycine.

Objectifs: Déterminer la fréquence de co-prescription d'un CNI et d'un macrolide chez les receveurs d'une greffe rénale, la proportion de patients ayant fait l'objet d'un suivi post-prescription et le risque d'effets indésirables attribuables aux médicaments.

Type d'étude: Une étude de cohorte rétrospective

Cadre: Les banques de données couplées du système de santé de l'Alberta (Canada).
Sujets: Nous avons inclus 293 adultes receveurs d'un rein entre 2008 et 2015 et à qui on avait co-prescrit un CNI et un macrolide.
Mesures: Le principal résultat attendu était une combinaison d'hospitalisation toutes causes, d'insuffisance rénale aigüe (hausse minimale de 0,3 mg/dL de la créatinine sérique ou équivalente à 1,5 fois la valeur mesurée initialement), ou de décès du patient dans les 30 jours suivant la prescription d'un macrolide.
Méthodologie: Nous avons répertorié les co-prescriptions CNI-macrolide et comparé les résultats des patients traités par clarithromycine/érythromycine à ceux traités avec l'azithromycine. Nous avons employé un modèle linéaire à effets mixtes pour établir les variations moyennes dans les mesures de créatinine sérique et de DFGe.
Résultats: Des 293 receveurs d'un rein ayant reçu une co-prescription CNI-macrolide, 38 % (n = 112) ont été traités avec la clarithromycine/érythromycine et 62 % (n = 181) avec l'azithromycine. Les patients ayant reçu de la clarithromycine/érythromycine étaient moins susceptibles de faire l'objet d'un suivi ambulatoire du taux de créatinine sérique post-prescription (56 % contre 69 % pour l'azithromycine, p = 0,03). Aucune différence significative n'a été observée entre les deux groupes quant au principal résultat attendu (17 % contre 11 %; p = 0,11). Cependant, les patients traités par clarithromycine/érythromycine présentaient un risque supérieur d'hospitalisation toutes causes (10 % contre 3 %; p = 0,02), et la moyenne de décroissance du DFGe pour ces patients était significativement supérieure (-5,4 mL/min/1,73 m^2 contre -1,9 mL/min/1,73 m^2 pour l'azithromycine; p < 0,05).
Limites: Nous n'avions pas les niveaux de CNI corrélés avec le moment de la co-prescription CNI-macrolide, ni les indications justifiant l'ordonnance de macrolide.
Conclusion: La clarithromycine et l'érythromycine ont été fréquemment co-prescrites aux receveurs d'une greffe rénale traités avec des CNI, malgré la connaissance des interactions médicamenteuses. Les patients recevant de la clarithromycine/érythromycine sont plus susceptibles d'être hospitalisés que ceux recevant de l'azithromycine. L'adoption de pratiques de prescription plus sûres est justifiée chez les receveurs d'une greffe rénale.

Keywords
adverse drug event, macrolide, calcineurin inhibitor, kidney transplant

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What was known before

Calcineurin inhibitors (CNI), such as cyclosporine and tacrolimus, are critical for kidney transplant immunosuppression, but have multiple potential drug interactions, such as with macrolide antibiotics. The CNIs are known to interact with clarithromycin and erythromycin, but not azithromycin. Case reports have shown rises in CNI levels in the setting of clarithromycin or erythromycin co-prescription. Whether this interaction results in significant clinical complications in real-world practice is currently unknown.

What this adds

Our study is the largest cohort study to date looking at CNI-macrolide interactions in kidney transplant recipients. Our results suggest that despite known drug interactions, clarithromycin and erythromycin are frequently co-prescribed in kidney transplant recipients on CNIs. These co-prescriptions are associated with adverse clinical outcomes, and safer prescribing practices in kidney transplant recipients are warranted.

Introduction

For eligible patients with end-stage renal disease (ESRD), kidney transplantation is the preferred treatment option as it is associated with improved long-term survival, better quality of life, and lower health care costs compared with chronic dialysis.[1,2] However, maintaining long-term allograft function requires use of immunosuppression. For the majority of recipients, maintenance immunosuppression consists of a combination of calcineurin inhibitors (CNIs, such as cyclosporine or tacrolimus), anti-proliferative agents (such as mycophenolate or azathioprine), and possibly corticosteroids.[3,4] With the advent of cyclosporine and tacrolimus, CNI-based regimens have significantly increased the rate of graft survival, decreased the incidence of acute rejection, and have become the first-line agent for maintenance immunosuppression.[3,5,6] However, CNIs have

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potential side-effects, including nephrotoxicity and neurotoxicity, as well as an increased risk of infections and malignancies.[7] Risk of adverse drug events with CNIs can increase with the co-prescription of certain medications. Cyclosporine and tacrolimus are metabolized by cytochrome P450 3A4 (CYP3A4) and P-glycoprotein, and drugs that inhibit or induce these systems can lead to complications related to altered CNI metabolism.[7,8]

Macrolide antibiotics, such as clarithromycin, erythromycin, and azithromycin, are often used to treat atypical infections. This is relevant in kidney transplant recipients as they are at higher risk of various infections due to their immunosuppressed state.[9] Clarithromycin and erythromycin can inhibit the metabolism of CNIs by binding to CYP3A4.[10] Case reports describe a rise in CNI blood, serum, and plasma levels in the setting of a clarithromycin[11-15] or erythromycin[16-23] co-prescription. In contrast, azithromycin is a macrolide that is prescribed for similar indications as clarithromycin or erythromycin, but differs in that it does not inhibit CYP3A4 and is not associated with changes in CNI metabolism.[10,24]

Whether interactions between CNIs and macrolides result in significant complications in real-world practice is currently unknown. We conducted this study to determine the incidence and outcomes of CNI and macrolide co-prescriptions in kidney transplant recipients.

Materials and Methods

Design and Setting

We conducted a population-based, retrospective cohort study using linked health care databases within the Alberta Kidney Disease Network (AKDN), which incorporates data from Alberta Health, the provincial health ministry.[25] More than 99% of Alberta residents are registered with Alberta Health and have universal access to hospital care and physician services. This study followed guidelines for observational studies (Supplemental Table S1)[26] and the protocol was approved by the research ethics boards at the University of Alberta and the University of Calgary, with a waiver of patient consent granted.

Data Sources

We ascertained baseline characteristics, covariate information, and outcome data from the AKDN records (Supplemental Table S2). Kidney transplant recipients were identified from the Northern and Southern Alberta Renal Program databases (NARP and SARP), which provide care to all patients treated with chronic dialysis or kidney transplant in the province. The Alberta Health database contains information on demographics, vital statistics, and diagnostic and procedural information for inpatient and outpatient physician services. The Pharmaceutical Information Network (PIN) captures prescription drug information on all medications dispensed in Alberta and was used to identify prescriptions dispensed for immunosuppressive medications and antibiotics. These data sources were also linked to a provincial laboratory repository via unique, encoded, patient identifiers held by the AKDN. All inpatient, emergency, and outpatient serum creatinine values are available in the provincial laboratory data. These databases have been previously used for research on health outcomes and services.[27,28]

Population

We included all prevalent kidney transplant recipients between July 30, 2008, and March 1, 2015, in Alberta, Canada. We excluded pediatric recipients (<18 years old) and recipients of a previous organ transplant or a simultaneous multi-organ transplant, including kidney-pancreas. We also excluded recipients who did not have follow-up beyond the first year of their transplant, as there are frequent changes in the dose of immunosuppressive medications in the first year, making it difficult to attribute any observed risk of CNI toxicity to co-prescriptions. Recipients were excluded if they died or experienced primary nonfunction or graft failure within the first year of their transplant, as evidenced by the return to chronic dialysis. Thus, to be included in the study, recipients must have survived the first year of their transplant with a functioning graft.

We then identified recipients who, after their first post-transplant year, had evidence of a prescription dispensed for one of the study antibiotics (clarithromycin, erythromycin, or azithromycin). Only the first prescription for each recipient was considered and the date of the prescription served as the start date of follow-up (index date). We excluded recipients who filled >1 study antibiotic on the index date to compare mutually exclusive groups. To look at co-prescriptions with a study macrolide only, we excluded recipients who were prescribed combination treatment consisting of clarithromycin, amoxicillin, and lansoprazole, used in the treatment of *Helicobacter pylori* (*H pylori*) infections. We excluded recipients without continuous CNI therapy (defined as having evidence of at least two CNI prescriptions within 210 days before the index date) to confirm co-prescription of the study macrolide and CNI. We excluded recipients who had evidence of a hospital discharge within 2 days of their index date, to ensure new outpatient prescriptions were not continuation of inpatient treatments and to exclude recipients with serious infections requiring hospitalizations. The cohort creation is shown in Supplemental Figure S1. Similar methodologies have been used in studies looking at co-prescription of macrolides and statins[29,30] and macrolides and calcium channel blockers.[31]

Baseline Characteristics

Baseline characteristics were ascertained at the index date. Demographic data, including age and sex, were determined from the Alberta Health administrative data files. Postal codes were linked to the Canadian Census using the Postal Code Conversion file to determine median neighborhood household income quintile (level 5 being the highest) as well as rural versus urban location of residence.

Demographic data were complete except for income quintile (1.4% missing).

Transplant-related data such as pre-transplant dialysis modality and dialysis duration were determined from the NARP and SARP databases. Graft function at the index date was determined by calculating the estimated glomerular filtration rate (eGFR, based on the Chronic Kidney Disease Epidemiology Collaboration equation [CKD-EPI]) using the mean of all outpatient serum creatinine measurements within a 6-month look-back window prior to, and including, the index date.[32] Similarly, albuminuria was defined by all outpatient random spot urine measurements in the 6 months prior to and including the index date (albumin-creatinine ratio [ACR], protein-creatinine ratio [PCR], or urine dipstick). Albuminuria was categorized based on the Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease definition as normal/mild (A1: ACR $<$30 mg/g, PCR $<$150 mg/g, or dipstick negative or trace), moderate (A2: ACR 30-300 mg/g, PCR 150-500 mg/g, or dipstick 1+), or heavy (A3: ACR $>$300 mg/g, PCR $>$500 mg/g, dipstick $\geq$2+), as previously described.[25,28,33] For recipients with multiple albuminuria measurements in the 6 months prior to and including the index date, the median value was calculated.

The presence of one or more diagnostic code in the 3 years prior to and including the index date was used for identification of co-morbidities using validated *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) and *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*), coding algorithms applied to physician claims and hospitalization data.[34,35] Hypertension and diabetes mellitus were identified from hospital discharge records and physician claims based on validated algorithms.[36,37]

The PIN database was used to identify other immunosuppressive agents, such as anti-proliferative agents and corticosteroids, as well as other baseline medication use in the preceding 120 days, such as angiotensin-converting enzyme (ACE) inhibitors and diuretics.

Outcomes

Recipients were followed for 30 days after the index date to assess outcomes. The primary outcome was a composite of all-cause hospitalization, acute kidney injury (defined as $\geq$0.3 mg/dL serum creatinine increase or 1.5 times baseline using outpatient, inpatient, and emergency room serum creatinine measurements), or all-cause mortality. To assess post-prescription monitoring, we determined the proportion of recipients who had at least one outpatient serum creatinine measurement within 30 days of the index date. If at least one serum creatinine measurement was available, we examined the change in serum creatinine and eGFR between the baseline measurement and the highest serum creatinine value within 30 days of the index date.

Statistical Analyses

Recipients were followed from their index date (date of macrolide prescription) until the first of the outcome of interest, emigration from the province, end of study (March 31, 2015), or death for a maximum of 30 days. Categorical variables were expressed as absolute and relative frequencies and continuous variables were expressed as medians (interquartile range, IQR). We compared the outcomes between CNI users co-prescribed macrolides using azithromycin as the reference drug, as it is not associated with CNI drug interactions. We compared baseline characteristics and crude outcomes of clarithromycin or erythromycin users with azithromycin users by means of chi-square or Fisher exact tests, and Kruskal-Wallis test, as appropriate. We used logistic regression to examine the association of the exposure with the primary outcome and its composites, and serum creatinine measurements. We reported unadjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI). We used a linear mixed-effects model to examine the mean change separately in serum creatinine and eGFR, specifying fixed effects for the main effects of group, time (baseline and highest value within 30 days of the index date), and their interaction, as well as a random effect for the recipient. The 95% CI were bootstrapped, with 5000 replications, given the nonnormality of residuals. Statistical analyses were performed using Stata MP 13.1 (Stata Corporation, College Station, Texas). A P value of $<$.05 was used to define statistical significance. A schematic of the study design is presented in Supplemental Figure S2.

Results

Baseline Characteristics

There were 293 adult, kidney-only transplant recipients in our cohort who were co-prescribed a CNI and a macrolide during the study period. Baseline characteristics of the recipients at their index date are shown in Table 1. Almost 40% (n = 112) of recipients were prescribed clarithromycin or erythromycin, while the rest were prescribed azithromycin (n = 181). The median age was 55 years and the median eGFR was 58 mL/min/1.73 m^2 at the time of the macrolide prescription. Women were less likely to be prescribed clarithromycin or erythromycin compared with azithromycin (37% vs 53%, P = .006). Diabetes mellitus was also lower in clarithromycin or erythromycin users compared with azithromycin users (26% vs 40%, P = .01). Of the identifiable physicians, over half of the clarithromycin or erythromycin prescriptions were from general practitioners and the majority occurred in the earlier eras (2008-2013 vs 2014-2015). In contrast, nephrologists prescribed the majority of baseline ACE inhibitors, ARBs, and statins compared with general practitioners (59.3% vs 6.2%, 53.0% vs 9.6%, and 58.9% vs 6.6%, respectively). Recipients who were prescribed

Table 1. Baseline Characteristics of Kidney Transplant Recipients Co-Prescribed a Calcineurin Inhibitor and a Macrolide.

	Total n = 293	Clarithromycin or erythromycin n = 112	Azithromycin n = 181	*P* value
Demographics				
Median age, years	55.3 (44.8-64.5)	53.8 (42.4-64.7)	55.4 (45.2-63.3)	.4
Sex, female	137 (46.8)	41 (36.6)	96 (53.0)	.01
Socioeconomic status[a]				
Low	77 (26.3)	30 (26.8)	47 (26.0)	.5
Middle	46 (15.7)	22 (19.6)	24 (13.3)	
High	53 (18.1)	22 (19.6)	31 (17.1)	
Missing data	4 (1.4)	1 (0.9)	3 (1.7)	
Residence[b]				
Urban	254 (86.7)	95 (84.8)	159 (87.9)	.5
Rural	39 (13.3)	17 (15.2)	22 (12.2)	
Kidney-related characteristics				
Pre-transplant dialysis modality[c]				
Hemodialysis	146 (49.8)	52 (46.4)	94 (51.9)	.3
Peritoneal dialysis	79 (27.0)	35 (31.3)	44 (24.3)	
Preemptive	6 (2.1)	4 (3.6)	2 (1.1)	
Missing	62 (21.2)	21 (18.8)	41 (22.7)	
Dialysis duration, years	1.4 (0.7-2.4)	1.3 (0.7-2.5)	1.6 (0.7-2.4)	.3
Time since transplant, years[d]	7.8 (4.1-12.5)	7.3 (3.9-11.8)	7.8 (4.1-13.2)	.6
Northern program recipient	218 (74.4)	83 (74.1)	135 (74.6)	.9
Serum creatinine (mg/dL)[e]	1.2 (1.0-1.6)	1.3 (1.1-1.6)	1.2 (1.0-1.7)	.3
eGFR (mL/min/1.73 m^2)[e]	57.6 (42.1-72.3)	54.2 (43.7-76.0)	57.9 (42.1-69.5)	.7
≥90	20 (6.8)	9 (8.0)	11 (6.1)	.9
60-89	110 (37.5)	40 (35.7)	70 (38.7)	
30-59	131 (44.7)	50 (44.7)	81 (44.8)	
15-29	22 (7.5)	9 (8.0)	13 (7.2)	
<15	3 (1.0)	1 (0.9)	2 (1.1)	
Missing	7 (2.2)	3 (2.7)	4 (2.2)	
Albuminuria[e]				
Normal/mild	211 (72.0)	86 (76.8)	125 (69.1)	.4
Moderate	34 (11.6)	11 (9.8)	23 (12.7)	
Severe	37 (12.6)	10 (8.9)	27 (14.9)	
Missing	11 (3.8)	5 (4.5)	6 (3.3)	
Co-morbidities[f]				
Hypertension	188 (64.2)	72 (64.3)	116 (64.1)	.9
Diabetes mellitus	102 (34.8)	29 (25.9)	73 (40.3)	.01
Myocardial infarction	4 (1.4)	1 (0.9)	3 (1.7)	>.9
PCI or CABG	4 (1.4)	1 (0.9)	3 (1.7)	>.9
Heart failure	8 (2.7)	3 (2.7)	5 (2.8)	.6
Atrial fibrillation	9 (3.1)	4 (3.6)	5 (2.8)	.5
Stroke or TIA	10 (3.4)	5 (4.5)	5 (2.8)	.3
Peripheral vascular disease	10 (3.4)	3 (2.7)	7 (3.9)	.4
Cancer	26 (8.9)	9 (8.0)	17 (9.4)	.7
Charlson comorbidity index	3 (2, 4)	3 (2, 4)	3 (2, 4)	.7
Drug-related characteristics				
Year of cohort entry				
2008-2010	117 (39.9)	47 (42.0)	70 (38.7)	.02
2011-2013	121 (41.3)	53 (47.3)	68 (37.6)	
2014-2015	55 (18.8)	12 (10.7)	43 (23.8)	

(Continued)

Table 1. (Continued)

	Total n = 293	Clarithromycin or erythromycin n = 112	Azithromycin n = 181	*P* value
Drug-related characteristics				
Study antibiotic prescriber				
General practice	152 (51.9)	68 (60.7)	84 (46.4)	.1
Nephrologist	3 (1.0)	1 (0.9)	2 (1.1)	
Other	15 (5.1)	5 (4.5)	10 (5.5)	
Missing	123 (42.0)	38 (33.9)	85 (47.0)	
Immunosuppression use				
Cyclosporine	63 (21.5)	27 (24.1)	36 (19.9)	.4
Tacrolimus	213 (72.7)	76 (67.9)	137 (75.7)	.1
Prednisone	207 (70.7)	79 (70.5)	128 (70.7)	.9
MMF	128 (43.7)	63 (56.3)	65 (35.9)	.001
Myfortic	74 (25.3)	22 (19.6)	52 (28.7)	.08
Azathioprine	51 (17.4)	10 (8.9)	41 (22.7)	.003
Sirolimus	11 (3.8)	2 (1.8)	9 (5.0)	.2
Medication use				
ACE/ARB	182 (62.1)	78 (69.6)	104 (57.5)	.04
Diuretic (loop/nonloop)	91 (31.1)	37 (33.0)	54 (29.8)	.6
Beta-blockers	113 (38.6)	48 (42.9)	65 (35.9)	.24
Dihydropyridine CaCB	110 (37.5)	43 (38.4)	67 (37.0)	.8
Nondihydropyridine CaCB	19 (6.5)	10 (8.9)	9 (5.0)	.2
Statins	151 (51.5)	52 (46.4)	99 (54.7)	.17
Fibrates	7 (2.4)	3 (2.7)	4 (2.2)	>.99
Ezetimibe	9 (3.1)	3 (2.7)	6 (3.3)	>.99
NSAIDs	16 (5.5)	6 (5.4)	10 (5.5)	.9

Note. Data are presented as n (%) or median (interquartile range). eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA = transient ischemic attack; MMF = mycophenolate mofetil; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CaCB = calcium channel blocker; NSAIDs = nonsteroidal anti-inflammatory drugs; ACR = albumin-creatinine ratio; PCR = protein-creatinine ratio; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; KDIGO = Kidney Disease: Improving Global Outcomes.

[a]Income was categorized according to fifths of average neighborhood income (1 = lowest, 5 = highest).

[b]Urban location indicates a population >10 000 or population >1000 with population density >400/km^2.

[c]Fifty-three recipients initially identified as missing were able to be re-classified to hemodialysis (n = 33) and peritoneal dialysis (n = 20) after assessing for presence of dialysis codes.

[d]For prevalent recipients as of January 2001 whose date of transplant could not be determined (n = 27), the date of transplant was set to April 1, 1994.

[e]Mean serum creatinine and eGFR and median albuminuria (ACR, PCR, or urine dipstick) were calculated using all outpatient measurements within 6 months before and including the index date. eGFR was calculated using the CKD-EPI equation.[32] Albuminuria was categorized based on the KDIGO guidelines.[33] To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

[f]Assessed by the presence of a diagnostic or procedural code in the 3 years prior to and including the index date, except for hypertension, diabetes, heart failure, atrial fibrillation, and cancer (lymphoma, solid tumor, and metastatic) which were defined using a validated algorithm.[34,36-39]

clarithromycin or erythromycin were more likely to be on mycophenolate mofetil and an ACE inhibitor and less likely to be on azathioprine, compared with recipients who were prescribed azithromycin.

Outcomes

The odds of having an outpatient serum creatinine measurement within 30 days of the macrolide prescription were 41% less likely for clarithromycin or erythromycin users compared with azithromycin users (56% vs 69%, absolute risk difference = 13%; OR = 0.59, 95% CI = 0.36-0.96, P = .03) (Table 2). There was no significant difference in the primary outcome (composite of all-cause hospitalization, acute kidney injury, and death) between clarithromycin or erythromycin and azithromycin users (17% vs 11%, absolute risk difference = 6%; OR = 1.74, 95% CI = 0.88-3.46, P = .1). The risk of all-cause hospitalization was 3 times higher in the clarithromycin or erythromycin group compared with the azithromycin group (10% vs 3%, absolute risk difference = 7%; OR = 3.18, 95% CI = 1.14-8.84, P = .02). There was no significant difference between the two groups in acute kidney injury based on our definition; however, the mean decrement in eGFR was significantly greater in the clarithromycin or erythromycin versus azithromycin group (−5.4 vs −1.9 mL/min/1.73 m^2, $P < .05$).

Table 2. Outcomes Within 30 Days of Co-Prescription of a Calcineurin Inhibitor and a Macrolide.

Outcome	Total n = 293	Clarithromycin or erythromycin n = 112	Azithromycin (referent drug) n = 181	Unadjusted OR (95% CI)	*P* value[a]
Serum creatinine measurement	187 (63.8)	63 (56.3)	124 (68.5)	0.59 (0.36-0.96)	.03
Primary outcome[b]	38 (13.0)	19 (17.0)	19 (10.5)	1.74 (0.88-3.46)	.1
Hospitalization	17 (5.8)	11 (9.8)	6 (3.3)	3.18 (1.14-8.84)	.02
Acute kidney injury[c]	33 (11.3)	16 (14.3)	17 (9.4)	1.61 (0.78-3.33)	.2

Note. Data are presented as n (%) unless otherwise specified. CI = confidence interval; OR = odds ratio.
[a]*P* value was from the χ^2 test.
[b]Primary outcome was a composite of all-cause hospitalization, acute kidney injury, and death.
[c]Acute kidney injury was defined as ≥0.3 mg/dL serum creatinine increase or 1.5 times baseline.

Discussion

In this retrospective cohort study of almost 300 kidney transplant recipients, we found that 38% of macrolide prescriptions were for clarithromycin or erythromycin despite known drug interactions with CNIs. These recipients were less likely to receive post-prescription serum creatinine measurements than those who were prescribed azithromycin. In addition, all-cause hospitalization was significantly higher in clarithromycin or erythromycin users compared with azithromycin users. The small number of events, particularly death within 30 days, may have contributed to the lack of a statistically significant difference between the two groups for the primary composite outcome. Although there was no difference between the two groups for acute kidney injury, the mean decrement in eGFR was significantly greater in clarithromycin or erythromycin users versus azithromycin users.

Our results are consistent with previous case reports and case series of kidney transplant recipients reporting increases in CNI levels and serum creatinine with the co-prescription of clarithromycin or erythromycin.[11,13-20,23,40-42] By inhibiting intestinal and hepatic CYP3A4, clarithromycin and erythromycin alter CNI metabolism and increase serum concentrations of CNIs.[43] The CNI concentrations can increase 1.6- to 6-fold within 2 to 6 days of starting clarithromycin and 1.6- to 5-fold within 1 to 18 days of initiating erythromycin.[43] Acute CNI nephrotoxicity can result in acute arteriolopathy due to vasoconstriction of afferent arterioles, isometric vacuolization of the tubular cytoplasm, as well as *de novo* thrombotic microangiopathy seen on kidney biopsy.[44] In contrast, azithromycin does not affect CYP3A4 or produce enzyme/metabolite complexes and is likely safer to prescribe than clarithromycin or erythromycin for patients on CNIs.[45]

Various drug interactions with macrolides have been reported, including interactions with benzodiazepines, carbamazepine, methylprednisolone, warfarin, as well as statins.[46] A 2013 retrospective cohort study in Ontario reported interactions between CYP3A4-metabolized statins (atorvastatin, simvastatin, or lovastatin) and clarithromycin and erythromycin, but not azithromycin.[29] Co-prescription of clarithromycin or erythromycin with a CYP3A4-metabolized statin was associated with a higher risk of hospitalization with rhabdomyolysis, acute kidney injury, and all-cause mortality within 30 days. This is similar to our findings of macrolide-CNI interaction in kidney transplant recipients, and further demonstrates the importance of monitoring for macrolide drug interactions even in nontransplant patients.

We found that post-prescription monitoring of serum creatinine was less likely to be done for clarithromycin or erythromycin users compared with azithromycin users. This may be due to a lack of awareness of this drug interaction in the general medical community. In addition, physicians who prescribe azithromycin may be more aware of possible interactions between macrolides and CNIs. This awareness may lead to more frequent monitoring and overall improved care and reduced rate of hospitalizations. Although a proportion of prescriber information was missing, we found that the majority of macrolide prescriptions in kidney transplant recipients were from general practitioners and a minority were from nephrologists. This was despite nephrologists prescribing the majority of other medications, such as ACE inhibitors, ARBs, and statins. Educational sessions at general medical conferences may be one way of increasing awareness of macrolide drug interactions. Utilizing allied health professionals, such as pharmacists, to screen for macrolide drug interactions at the time of prescription fill may also be effective. Similarly, transplant nephrologists can educate their patients of these drug interactions with instructions to connect with their transplant team when prescribed a new antibiotic. Overall, the absolute number of serious adverse outcomes of macrolide-CNI co-prescriptions was low. This suggests that these risks can be managed with the appropriate macrolide and frequent monitoring, when such an antibiotic is required in the setting of CNI use.

Our study has several strengths. It is the largest cohort study to date looking at CNI-macrolide interactions in kidney transplant recipients over a 7-year period. Importantly, it illustrates real-world adverse outcomes as well as physician prescribing patterns of macrolides in kidney transplant recipients. In addition, the serum creatinine measurements obtained in our databases have been standardized across provincial laboratories, reducing inter-laboratory variation in measurements. We also incorporated use of validated diagnostic codes in our study.[36-39,47-50]

Our study also has limitations worth noting. We did not have access to serum CNI levels to correlate with the timing of CNI-macrolide co-prescription. However, we did have baseline serum creatinine and eGFR measurements for nearly all recipients, with less than 3% missing data. The indications for macrolide prescription are not recorded in the study data, and we did not have information regarding antibiotic allergies or the results of relevant cultures or susceptibilities. Therefore, we cannot exclude serious infections as the sole cause for adverse outcomes, although we did exclude recipients with recent hospitalizations. We did exclude cases of combination treatment of clarithromycin, amoxicillin, and lansoprazole commonly used in the treatment of *H pylori* infections. It is also possible that recipients filled a macrolide prescription without taking it, such as in the case for prophylactic prescription for traveler's diarrhea. Our study includes kidney recipients from one large Canadian province, and thus our results may not be generalizable to other recipients, particularly those of non-Caucasian race. Given the retrospective design, there may have been confounding variables that we were not able to account for, although we were able to measure numerous variables associated with our outcomes. Finally, as we included recipients who had a functioning graft at 1 year, there is potential for survival bias.

In conclusion, in this cohort of almost 300 kidney transplant recipients who were prescribed a macrolide while taking CNI-based immunosuppression, clarithromycin and erythromycin were commonly used, despite known drug interactions with CNIs and potential for adverse events. In addition, these recipients were less likely to receive post-prescription monitoring of serum creatinine compared with recipients who were prescribed azithromycin. These results suggest that further education and awareness is required to prevent adverse drug events in kidney transplant recipients.

List of Abbreviations

ACR, albumin-creatinine ratio; ACE, angiotensin-converting enzyme; AKDN, Alberta Kidney Disease Network; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CNIs, calcineurin inhibitors; CYP3A4, cytochrome P450 3A4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; *H pylori, Helicobacter pylori; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Statistical Classification of Diseases, Tenth Revision*; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; NARP, Northern Alberta Renal Program; OR, odds ratio; PCR, protein-creatinine ratio; PIN, Pharmaceutical Information Network; SARP, Southern Alberta Renal Program.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the research ethics boards at the University of Alberta and the University of Calgary, with a waiver of patient consent granted.

Consent for Publication

All authors reviewed the final manuscript and consented for publication.

Availability of Data and Materials

Data and materials may be made available upon written request to the corresponding author.

Authors' Note

This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta nor Alberta Health or Alberta Health Services express any opinion in relation to this study.

Author Contributions

All authors conceived of the study. R.J., A.L., and N.N.L. participated in data acquisition, data analysis and interpretation. R.J. drafted the article. All authors revised the article and accepted accountability for the integrity of the data and data analysis.

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