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ORIGINAL ARTICLE

Mtor inhibitors associated with higher cardiovascular adverse events—A large population database analysis

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Abstract

There are limited real-world data available regarding adverse events (AEs) of immunosuppressants. We utilized the FDA Adverse Event Reporting System (FAERS) database from 2004 to 2018 to perform a retrospective database analysis. We analyzed AE reports due to the individual agents tacrolimus, sirolimus, or everolimus and compared reporting odds ratios of the mTOR inhibitors to tacrolimus. The mTOR inhibitors arm had 1282 reports with 4176 AEs, while the tacrolimus arm had a total of 7587 reports with 20 940 individual AEs. mTOR inhibitors had significantly higher incidences of cardiovascular (ROR 1.95, 95% CI 1.70, 2.23), dermatologic (ROR 1.34, 95% CI 1.04, 1.73), endocrine (ROR 1.52, 95% CI 1.26, 1.82), gastrointestinal (ROR 1.15, 95% CI 1.01, 1.30), infectious disease (ROR 1.35, 95% 1.20, 1.52), musculoskeletal (ROR 1.39, 95% CI 1.13, 1.70), pulmonary (ROR 3.46, 95% 2.97, 4.03), renal (ROR 1.27, 95% CI 1.10, 1.46), and vascular AEs (ROR 3.10, 95% CI 2.14, 4.49). Across every organ type, mTOR inhibitors had greater cardiovascular AEs compared to tacrolimus, specifically in arteriosclerosis, heart failure, hypotension, tachycardia, chest pain, edema, and pericardial disorders. mTOR inhibitors may be associated with higher cardiovascular AEs. Further investigation is required to determine the potential mechanism of this effect.

KEYWORDS
adverse drug reaction, immunosuppression, mammalian target of rapamycin inhibitor, sirolimus, tacrolimus

1 | INTRODUCTION

The management of immunosuppressive therapy requires a delicate balance between maximizing immunosuppression to prevent rejection while minimizing the complications of immunodeficiency and the adverse effects (AEs) of therapy. One of the biggest challenges in immunosuppressive management is the acute and chronic nephrotoxicity associated with calcineurin inhibitors (CNIs). Moreover, CNIs have been associated with the development of multiple cardiovascular disease risk factors including hypertension, hyperlipidemia, and new-onset diabetes after transplantation.[1] Metabolic syndrome induced by immunosuppressants is a significant cause of mortality and morbidity. The use of mammalian target of rapamycin (mTOR) inhibitors in maintenance immunosuppression has been increasing steadily in solid organ transplantation in recent years due to their unique mechanism of action and safety profiles. There are limited real-world data available regarding AEs of immunosuppressants, especially for the newer mTOR inhibitors sirolimus and everolimus, which were approved in 1999 and 2009, respectively.

The FDA Adverse Event Reporting System (FAERS) database was created to support FDA's postmarketing surveillance on drugs and biologic therapeutics. It contains adverse reaction and medication error reports sent to the FDA through MedWatch, the FDA Safety Information and Adverse Event Reporting Program. The FDA

receives over one million AE and medication error reports every year from healthcare professionals and consumers.[2] Our study aimed to identify and characterize AEs reported for immunosuppressants in solid organ transplant patients utilizing this large real-world database.

2 | METHODS

This study utilized the FAERS database and its legacy version, Adverse Effect Reporting System (AERS), to perform a retrospective data analysis. Because the FAERS database contains de-identified patient information, our study was exempted from the IRB approval process. Reporting to FAERS database is voluntary and can be done by physicians, pharmacists, nurses, other healthcare professionals, patients, family members, and legal representatives. If any party reports an AE to the manufacturer, the manufacturer is mandated to forward the report to the FDA. Data are in quarterly format for AERS from the first quarter of 2004 to the third quarter of 2012 and for FAERS from the fourth quarter of 2012 to the second quarter of 2018.[3] Data from FAERS are available online at: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files. The data were homogenized by modifying original text tables to produce a consistent table field structure. The combining was performed by individually downloading the FAERS quarterly reports in dollar separated text format (*.TXT). The names of the columns were also homogenized, and the columns missing from older releases were added with empty values.[3] All the quarterly files were combined into a master file, which was used as the primary source for analysis. A translational dictionary was created to streamline data searching. For example, by searching with the keyword "tacrolimus", our program pooled all reports containing "tacrolimus", "Envarsus", "Astagraf", and "Prograf" from the master file. Variations such as capitalizations and misspellings were still recognized and assigned to "tacrolimus." We included patients on immunosuppression for kidney, liver, heart, and lung transplantations. In order to isolate AEs due to specific agents, we analyzed reports due to the individual agents tacrolimus, sirolimus, or everolimus and compared reporting odds ratios (ROR) of the mTOR inhibitors to tacrolimus (Figure 1). Reported AEs deemed to be unrelated to medication therapy were excluded. AEs were grouped into 17 main system-based groups using the Medical Dictionary for Regulatory Activities (MedDRA) terminologies: cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, hematologic, immunologic, infectious disease, malignancies, musculoskeletal, neurologic, ophthalmic, otic, psychiatric, pulmonary, renal, reproductive, and vascular. We further subdivided cardiovascular AEs into 17 subgroups: arrhythmias, arteriosclerosis, abnormal blood pressure, bradycardia, cardiac arrest, chest pain, edema, heart block, heart failure, hypertension, hypotension, nonspecific cardiac disorders, pericardial disorders, QT prolongation, syncope, tachycardia, and valvular disorders.

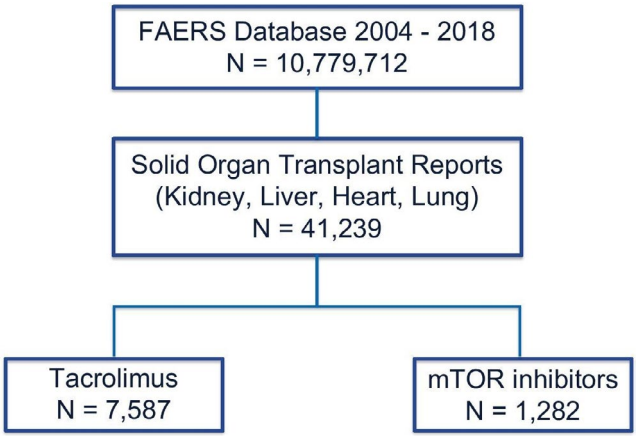

FIGURE 1 Study design. Our study utilized the FDA Adverse Event Reporting System (FAERS) database from 2004 through the second quarter of 2018 to perform a retrospective data analysis. We included adverse events reported for tacrolimus and mTOR inhibitors in kidney, liver, heart, and lung transplant recipients

2.1 | Statistical analysis

Frequency for each side effect was calculated by the equation:

$$\text{Reporting frequency} = \frac{\text{Number of Records of AEs}}{\text{Number of Patients Records}}$$

AE report rates were compared via the Ln Reporting Odds Ratio (LnROR) using the following equations:

$$\text{ROR} = \frac{ad}{bc}$$

a = Number in exposed group with an adverse event
b = Number in exposed group with no adverse event.
c = Number in control group with the adverse event.
d = Number in control group with no adverse event.
LnROR was defined and calculated by the following equation:

$$\text{LnROR} = \text{Ln}(\text{ROR})$$

Standard error (SE) of the LnROR value was calculated by the following equation:

$$\text{SE}_{\text{LnROR}} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

Error bars were calculated using 95% confidence interval:
95% CI = $[e^{(\text{LnROR} - 1.96(\text{SE}_{\text{LnROR}}))}, e^{(\text{LnROR} + 1.96(\text{SE}_{\text{LnROR}}))}]$.

3 | RESULTS

The mTOR inhibitors arm had 1282 reports with 4176 AEs, while the tacrolimus arm had a total of 7587 reports with 20 940 individual AEs. The majority of the reports were from kidney and liver transplants, making up 88% and 79% of tacrolimus and mTOR inhibitors

reports, respectively. Lung had the fewest numbers of reports, 4% in each arm (Figure 2). According to United Network for Organ Sharing (UNOS) data, we performed a total of 36 530 transplants nationally in 2018, 58% of which were kidney, 23% liver, 9% heart, and 7% lung. The number of reports in the FAERS database during our study period reflected the national transplanted organs trend.

mTOR inhibitors had significantly higher incidences of cardiovascular (ROR 1.95, 95% CI 1.70, 2.23), dermatologic (ROR 1.34, 95% CI 1.04, 1.73), endocrine (ROR 1.52, 95% CI 1.26, 1.82), gastrointestinal (ROR 1.15, 95% CI 1.01, 1.30), infectious disease (ROR 1.35, 95% 1.20, 1.52), musculoskeletal (ROR 1.39, 95% CI 1.13, 1.70), pulmonary (ROR 3.46, 95% 2.97, 4.03), renal (ROR 1.27, 95% CI 1.10, 1.46), and vascular AEs (ROR 3.10, 95% CI 2.14, 4.49) compared to that of tacrolimus. In contrast, mTOR inhibitors had significantly lower reports for neurologic (ROR 0.66, 95% CI 0.55, 0.78), psychiatric (ROR 0.69, 95% CI 0.48, 0.99), and reproductive (ROR 0.66, 95% CI 0.46, 0.95). No differences were found for hematologic, immunologic, malignancies, ophthalmic, and otic. Detailed reporting frequencies are illustrated in Table 1 and Figure 3.

With respect to cardiovascular AEs, the mTOR inhibitors group had significantly higher incidences compared to tacrolimus group across every organ type (Figure 4). Within the subgroups in the cardiovascular category, mTOR inhibitors had significantly higher incidences in arteriosclerosis (ROR 1.48, 95% CI 1.04, 2.11), heart failure (ROR 2.12, 95% CI 1.56, 2.88), hypotension (ROR 2.90, 95% CI 1.79, 4.70), tachycardia (ROR 3.29, 95% CI 1.90, 5.70), chest pain (ROR 3.55, 95% CI 1.87, 6.75), edema (ROR 3.64, 95% CI 2.67, 4.96), and pericardial disorders (ROR 16.14, 95% CI 8.07, 32.29). No statistical differences were found with valvular disorders (ROR 0.44, 95% CI 0.10, 1.85), QT prolongation (ROR 0.61, 95% CI 0.19, 2.01), arrhythmias (ROR 0.66, 95% CI 0.36, 1.24), cardiac arrest (ROR 0.67, 95% CI 0.32, 1.39), heart block (ROR 1.18, 95% CI 0.26, 5.41), hypertension (ROR 1.21, 95% CI 0.80, 1.84), bradycardia (ROR 1.39, 95% CI 0.47, 4.15), and syncope (ROR 1.69, 95% CI 0.35, 8.15).

To explore the effect of transplanted organ on the reported AEs, we performed a subgroup analysis with cardiovascular AEs in which heart transplant reports were excluded. Despite this, mTOR inhibitors still had significantly higher cardiovascular incidences compared to tacrolimus group (ROR 1.66, 95% CI 1.42, 1.93). Arteriosclerosis was the only subgroup endpoint that changed from significant to insignificant (ROR 1.35, 95% CI 0.91, 2.00); other endpoints remained unchanged when excluding heart transplant reports. We also saw no correlation between electrolyte abnormalities or hyperglycemia and cardiovascular AEs. Reporting incidences for potassium and magnesium abnormalities were similar between mTOR inhibitors and tacrolimus, ROR 0.46 (95% CI 0.20, 1.06) and 0.95 (95% CI 0.33, 2.73), respectively, although potassium abnormalities were lower numerically with mTOR inhibitors and close to significance. Hyperglycemia was similar between the two groups: ROR 1.36, 95% CI 0.99, 1.86.

4 | DISCUSSION

Whether mTOR inhibitors are cardiotoxic or cardioprotective remains controversial. The known effects of mTOR inhibitors on lipids suggest that they may have detrimental effects on the cardiovascular system. mTOR inhibitors are well-recognized as a major cause of post-transplantation hyperlipidemia. They can increase high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides in 40%–75% of patients.[4] mTOR inhibition may induce upregulation of adipocyte fatty acid-binding protein expressed in macrophages and monocytes and therefore increase accumulation of triglycerides.[5] Sirolimus has also been shown to increase hepatic synthesis of triglyceride and secretion of very low-density lipoproteins[6]; and mTOR inhibitor-induced dyslipidemia is known to be reversible and dose-dependent. Our study confirmed the higher incidence of dyslipidemia associated with mTOR inhibitors compared to tacrolimus (ROR 12.15, 95% CI 7.00, 21.09). Data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial showed that in patients with type 2 diabetes and established coronary artery disease, elevated triglyceride level was independently associated with adverse cardiovascular outcomes.[7]

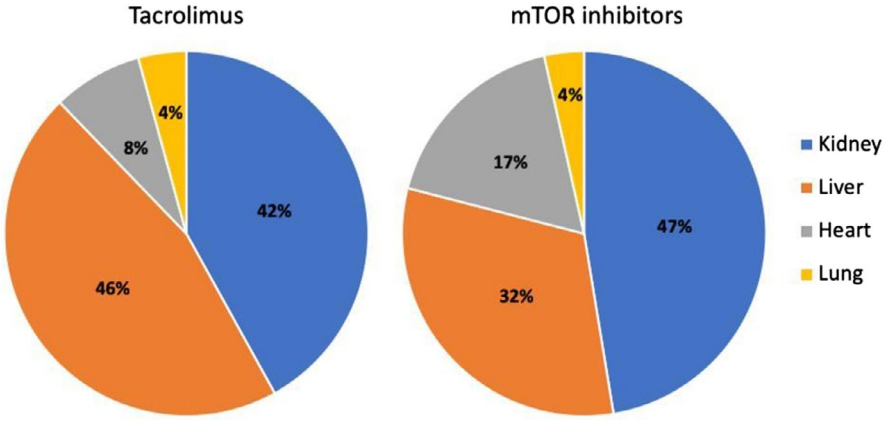

FIGURE 2 Reports by organ type. The tacrolimus arm had a total of 7587 reports with 20 940 individual adverse events, while the mTOR inhibitors arm had 1282 reports with 4176 adverse events. The majority of the reports were from kidney and liver transplants, while lung had the fewest numbers of reports

System	Tacrolimus (%)	mTOR inhibitors (%)	Reporting Odds Ratio (95% CI)
Cardiovascular	13.38	26.05	1.95 (1.70, 2.23)
Dermatologic	4.43	5.93	1.34 (1.04, 1.73)
Endocrine/Metabolic	8.19	12.40	1.52 (1.26, 1.82)
Gastrointestinal	25.54	29.33	1.15 (1.01, 1.30)
Hematologic	9.58	9.83	1.03 (0.84, 1.25)
Immunologic	1.56	2.26	1.45 (0.96, 2.19)
Infectious Disease	25.21	34.01	1.35 (1.20, 1.52)
Malignancies	7.54	8.97	1.19 (0.97, 1.47)
Musculoskeletal	6.87	9.52	1.39 (1.13, 1.70)
Neurologic	19.61	12.87	0.66 (0.55, 0.78)
Ophthalmic	3.53	2.65	0.75 (0.52, 1.08)
Otic	0.41	0.47	1.15 (0.48, 2.75)
Psychiatric	3.84	2.65	0.69 (0.48, 0.99)
Pulmonary	6.79	23.48	3.46 (2.97, 4.03)
Renal	16.87	21.37	1.27 (1.10, 1.46)
Reproductive	3.90	2.57	0.66 (0.46, 0.95)
Vascular disorder	1.11	3.43	3.10 (2.14, 4.49)

TABLE 1 Reporting frequency and odds ratio of mTOR inhibitors compared to tacrolimus. mTOR inhibitors had significantly higher incidences of cardiovascular, dermatologic, endocrine, gastrointestinal, infectious disease, musculoskeletal, pulmonary, renal, and vascular adverse events compared to that of tacrolimus

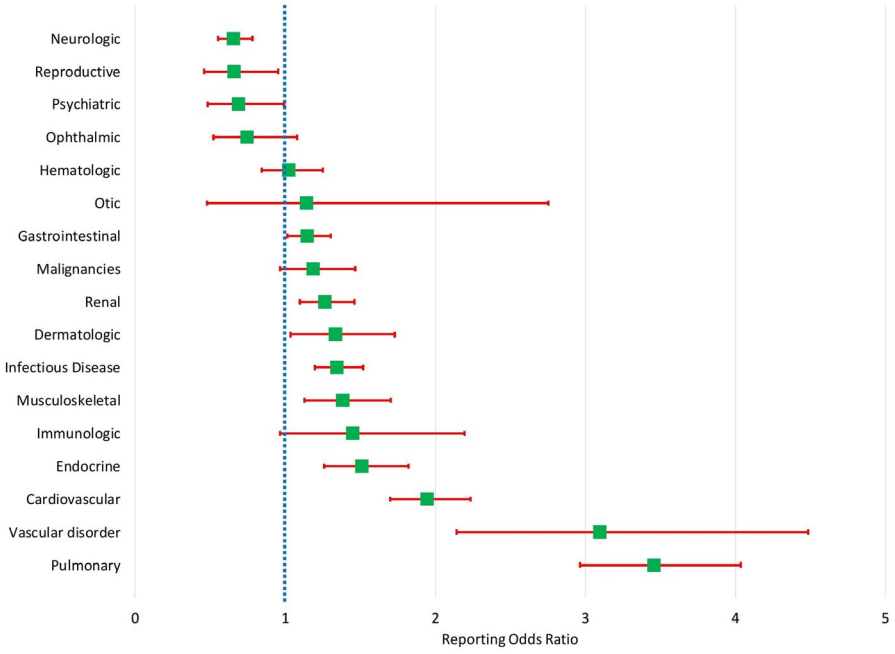

FIGURE 3 Reporting Odds Ratio (mTORi/Tacrolimus). mTOR inhibitors had significantly higher incidences of cardiovascular, dermatologic, endocrine, gastrointestinal, infectious disease, musculoskeletal, pulmonary, renal, and vascular adverse events compared to that of tacrolimus

mTOR is an atypical serine/threonine kinase which forms two downstream protein complexes, mTOR complex 1 and mTOR complex 2.[8] mTOR is a key regulator of cardiovascular physiology and pathology. mTOR complex 1 has been shown to be crucial for cardiac adaptation to pressure overload and development of compensatory hypertrophy.[8] On the contrary, there is evidence to suggest that mTOR inhibitors might be cardioprotective. T cells and macrophages play important roles in the progression from atherosclerotic plaque initiation to rupture. Sirolimus limits vascular smooth muscle cell proliferation and immune cell involvement at the site of vascular lesions.[9] Animal models have also suggested that mTOR inhibitors can prevent lipid accumulation in tissues and help stabilize atherosclerotic plaques independent of serum lipid level.[10-13] Coronary stents coated with mTOR inhibitors are used routinely in percutaneous coronary intervention based on animal data showing that mTOR inhibitors can attenuate intimal thickening and therefore reduce incidence of stent restenosis.[14] In heart transplant recipients, mTOR inhibitors have consistently demonstrated beneficial effects on cardiac allograft vasculopathy (CAV). As a result of the accumulation of inflammatory cells and lipid deposition, CAV is an accelerated fibroproliferative disease.[15] CAV pathophysiology involves both immune factors such as T-cell-secreting cytokines and human

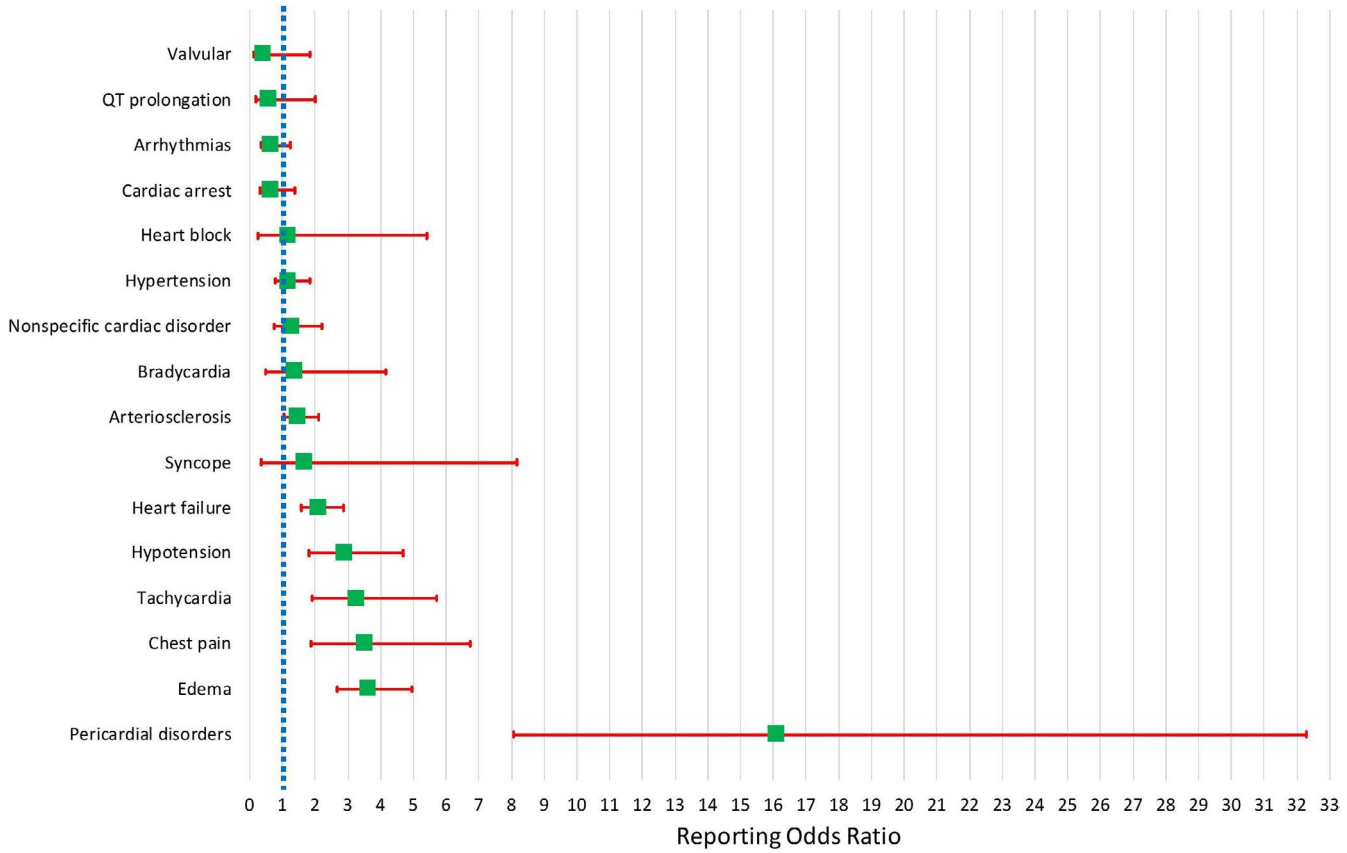

FIGURE 4 Reporting Odds Ratio (mTORi/Tacrolimus) for cardiovascular events. mTOR inhibitors had significantly higher incidences in arteriosclerosis, heart failure, hypotension, tachycardia, chest pain, edema, and pericardial disorders

leukocyte antigens antibodies, as well as nonimmune factors. mTOR inhibitors, whether in combination with reduced-dose CNI therapy or in the de novo setting, resulted in a 61% relative risk reduction in CAV when compared to a CNI-based regimen.[16] Interestingly, the effects of mTOR inhibitors on attenuating CAV progression seemed to be independent of LDL cholesterol levels. One single-center study demonstrated differential effects of sirolimus and CNI-based immunosuppression on CAV progression in heart transplant patients. Conversion to sirolimus as primary immunosuppression appeared to negate the deleterious effects of elevated LDL on CAV progression, whereas, in patients maintained on CNI therapy, LDL cholesterol level was important for determining the severity of CAV.[17]

Nevertheless, whether results from animal models and heart transplant recipients can be extrapolated to other transplant patient populations is debatable. Cardiovascular mortality remains the leading cause of death in kidney transplant recipients at one and ten years post-transplant.[18] In a retrospective study including 210 327 kidney transplant recipients who received their first kidney transplant from 1996 to 2014, cardiovascular deaths accounted for 24.7% of all-cause mortality.[19] Studies investigating cardiovascular outcomes in kidney and liver transplant patients are scarce. One registry study using UNOS data demonstrated an increased overall mortality in kidney transplant recipients with an mTOR inhibitor-based regimen compared with those who received CNI-based regimens.[20] In another meta-analysis evaluating 21 randomized controlled trials comparing immunosuppressive regimens with and without sirolimus in kidney transplant recipients, mTOR inhibitors were associated with 43% increased risk of mortality, with a higher proportion of death due to infection and cardiovascular disease.[21] In contrast, in a long-term follow-up of the MECANO trial, no significant differences in cardiovascular events and mortality were found between mTOR inhibitors and a CNI-based regimen in kidney transplant recipients after 7 years follow-up.[22] One retrospective study with 1812 liver recipients investigated cardiovascular outcomes in sirolimus versus control.[9] There were no differences in myocardial infarction, abdominal aortic aneurysm, cerebrovascular accident, and congestive heart failure incidences between the two groups. However, the sirolimus cohort was older, with higher proportions of pre-transplantation hypertension and diabetes and post-transplantation hypertension compared to non-sirolimus controls, which might suggest that sirolimus was cardioprotective despite the higher incidence of hypercholesterolemia.

It is irrefutable that mTOR inhibitors are associated with higher incidence of hyperlipidemia than CNIs, which is consistent with our study's finding. Nevertheless, we cannot establish a causal relationship between mTOR inhibitors and worse cardiovascular outcomes compared to CNIs with our large database analysis. As we lacked patient-level information, it is possible that the mTOR inhibitor group selected for more patients with existing cardiovascular disease. It is unclear whether mTOR inhibitors have negative or positive effects

on the heart and whether the drug-induced hyperlipidemia translates to a negative impact on cardiovascular outcomes. Therefore, it is crucial to have clinical trials with cardiovascular outcomes as primary endpoints in solid organ transplant recipients.

Utilizing this large population database covering 14 years of reports, we found that mTOR inhibitors were associated with more reported side effects compared to those of tacrolimus. This is consistent with the high discontinuation rate reported for mTOR inhibitors in the literature. In the ELEVATE trial where 715 de novo kidney transplant recipients were randomized at 10–14 week to convert to everolimus or remain on the standard CNI therapy, medication discontinuation due to AEs was more frequent with everolimus (23.6%) compared to the CNI arm (8.4%).[23] Moreover, a meta-analysis evaluating the use of mTOR inhibitors in heart transplant recipients found that mTOR inhibitors, whether in combination with reduced-dose CNI or with an antimetabolite, led to more than twice as many therapy discontinuations for side effects than the combination of a CNI with antimetabolites.[16] One possible explanation for this higher rate of side effects in mTOR inhibitors could be due to reporting bias. As mTOR inhibitors can impair wound healing, they are infrequently used de novo for post-transplant management. We expect that the majority of patients were introduced or switched to mTOR inhibitors later in the course of their transplant and therefore the AEs reported may have been increased. The higher incidence of AEs with mTOR inhibitors, particularly with respect to infectious, pulmonary, vascular, endocrine, and cardiovascular systems, may be an important consideration for individualizing therapy.

We also saw higher incidence of renal AEs with mTOR inhibitors in our study. Proteinuria is a well-recognized side effect of mTOR inhibitors. In vitro studies suggested that glomerular proteinuria can be attributed to direct toxicity of sirolimus to the glomerular podocyte-endothelial axis through the inhibition of vascular endothelial growth factor.[24] De novo focal segmental glomerulosclerosis lesion has been documented in patients receiving sirolimus, possibly through its effect on mTOR to decrease cell survival.[25] mTOR inhibitor-induced proteinuria has been demonstrated to be associated with CAV progression and increased all-cause mortality.[26] Our finding highlighted the importance of monitoring urinary protein in patients on mTOR inhibitors on a regular basis and consider discontinuation of the medication if the proteinuria is progressive. The higher renal AEs reported in the mTOR inhibitors cohort could also be explained by the patient population as mTOR inhibitors are often used to withdraw or minimize CNI exposure in patients with preexisting chronic renal insufficiency.

While the FAERS database holds enormous and promising data, it is not without limitations. The database lacks individual patient-level data such as comorbidities and concurrent medications; therefore, unreported confounding variables could have affected outcomes. Although a causation relationship cannot be established between the reported AE and the suspected medication, the associations found in our study can be hypothesis-generating. Moreover, the FDA does not receive reports for every AE associated with a medication due to the voluntary nature of the database; AEs could be under- or over-reported. To account for this limitation, we analyzed the reporting incidence rates and odds ratio to assess the significance of the differences between the two cohorts.

5 | CONCLUSIONS

We analyzed the safety profile of mTOR inhibitors and tacrolimus utilizing a large-scale population database with data spanning 14 years which found that mTOR inhibitors may be associated with more cardiovascular AEs. Our data are consistent with the hypothesis that hyperlipidemia may predispose patients to cardiovascular events. However, the increased cardiovascular AEs may not be entirely explained by dyslipidemia. The use of mTOR inhibitors may also disrupt the balance of mTOR complexes and impact cardiovascular physiology. Our study provides more evidence to a controversial body of literature and gives more data to provide guidance on the choice of immunosuppression in transplantation. Further analysis is required to determine the potential mechanism of this effect.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

None to disclose.

AUTHOR CONTRIBUTION

Vi N. Nguyen, PharmD, and Shirley M. Tsunoda, PharmD participated in research design, the performance of the research, data analysis, and in the writing of the paper. **Ruben Abagyan, PhD,** participated in research design, the performance of the research, data collection, data analysis, and in the writing of the paper.

DATA AVAILABILITY STATEMENT

There is no data statement.

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