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Original Research

Tacrolimus Related Acute Pancreatitis: An Observational, Retrospective, Pharmacovigilance Study

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ABSTRACT

Purpose: Recent case reports have drawn attention to the emergence of acute pancreatitis, a potentially life-threatening complication associated with tacrolimus. This study uses the Food and Drug Administration Adverse Event Reporting System (FAERS) to investigate the risk signal of acute pancreatitis associated with calcineurin inhibitors (CNIs), with a focus on tacrolimus.

Methods: We conducted an observational retrospective pharmacovigilance study utilizing the FAERS database, encompassing data from its inception to the third quarter of 2023. The assessment of the association between CNIs and acute pancreatitis was carried out using the Information Component (IC) and Reporting Odds Ratio (ROR). Logistic regression analysis was employed to elucidate factors contributing to fatal outcomes. All analyses were performed using R version 3.2.5.

Finding: We identified 221 cases of acute pancreatitis linked to CNIs. The median age of individuals experiencing acute pancreatitis induced by tacrolimus was 43, with a predominant occurrence among male patients. Our study showed a significant association between CNIs and acute pancreatitis (ROR 1.82 [1.60–2.08], IC 0.85 [3.66–3.92]). Comparing tacrolimus and cyclosporine, the signal for tacrolimus seemed to be higher. Further analysis revealed that, with the exception of patients aged 60 and above, the signal for tacrolimus remained stable. Contrastingly, the signal for cyclosporine was unstable and limited to the male group and individuals aged less than 20 years. In cases of CNIs-related acute pancreatitis, the mortality rate was 31.67% (70/221 cases). Logistic regression analysis indicated that a younger age acts as a protective factor for death due to CNIs-related acute pancreatitis (OR 0.943, 95% CI 0.915–0.972, $P = 0.000$).

Implications: Our study has identified a safety signal for tacrolimus in relation to acute pancreatitis. Additionally, we observed advanced age as a significant risk factor for tacrolimus-related acute pancreatitis, leading to mortality. Given the widespread use of tacrolimus, it is crucial for healthcare providers to be vigilant and informed about the potential association with acute pancreatitis.

Introduction

Tacrolimus, as a representative calcineurin inhibitor (CNI), has been widely employed over the last two decades as an immunosuppressant due to its suppressive effects on cell-mediated and humoral immune responses.[1] However, along with its extensive use in transplantation, various adverse effects have been identified over the years, encompassing neurotoxicity, hepatotoxicity, nephrotoxicity, and susceptibility to infections.[2]

Acute pancreatitis has been associated with immunosuppressive agents, with azathioprine being the most commonly implicated drug, followed by steroids, backed by substantial evidence.[3] However, conclusive evidence for the induction of pancreatitis by other immunosuppressive agents, such as CNIs including tacrolimus and cyclosporine, is lacking.[4] Additionally, pancreatitis is not listed as an adverse drug reaction on the product label of CNIs.[1] Notably, in recent years, several case reports have highlighted tacrolimus as a potential cause of acute pancre-

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atitis.[1,4–6] As of now, there have been no reported cases of cyclosporine-induced acute pancreatitis.

Acute pancreatitis is a severe, life-threatening condition that requires early recognition and management, particularly in high-risk patients, including post-transplant individuals.[7] However, the clinical significance of tacrolimus-induced pancreatitis has not received adequate attention. Large-scale studies on CNIs causing acute pancreatitis have not been conducted in the past. It is crucial to acknowledge the available evidence in this field. Therefore, this study utilizes the Food and Drug Administration Adverse Event Reporting System (FAERS) database to perform a disproportionality analysis, comparing the reporting rate of acute pancreatitis, including tacrolimus and cyclosporine as immunosuppressive agents. Additionally, the study analyzes the clinical characteristics of CNI-induced acute pancreatitis and identifies risk factors for associated mortality. This aims to alert clinicians to the possibility of tacrolimus-induced acute pancreatitis during tacrolimus therapy.

Methods

Data Sources and Study variables

A retrospective observational pharmacovigilance study was conducted using data from the FAERS database. FAERS is a widely recognized and publicly available post-marketing safety surveillance database that comprises spontaneous adverse event (AE) reports submitted to the FDA. These reports come from healthcare professionals, individual patients, and pharmaceutical manufacturers across diverse regions and countries. The database covers data from Quarter 1 (Q1) of 2004 to the present, enabling early detection of safety signals and timely characterization of safety profiles, necessitating risk and benefit reassessment. The data files consist of seven datasets: demographic and administrative information (DEMO), drug details (DRUG), AEs (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates of drug therapy (THER), and indications (INDI).

This real-world, retrospective pharmacovigilance study is a disproportionality analysis based on FAERS database, collecting data from the first quarter (Q1) of 2004 to the third quarter (Q3) of 2023. Before data extraction and analysis, a systematic approach was employed to eliminate duplicated reports. To mitigate duplicate entries, only the most recent report for each patient was utilized, adhering to Food and Drug Administration (FDA) recommendations. The following details were retrieved: the safety report ID, patient characteristics (age, gender, reporting time, and reporting area), drug names, indication for treatment, AEs (including concomitant AEs), and outcomes. The above data retrieval work was conducted simultaneously by two researchers.

Drug Definition

We used generic and brand names which were listed in the Drugs@FDA Database to identify tacrolimus (ENVARSUS XR, PROGRAF, and PROTOPIC) and cyclosporine (ciclosporin, ciclosporine, CsA, ciclosporina, cyclosporin A, cyclosporine, ciclosporina).

Adverse Events Definition

Adverse events in the database were encoded in the preferred term (PT) using Medical Dictionary for Regulatory Activities terms (MedDRA). The search criterion employed was “Pancreatitis acute” [10033647] within the FAERS database. Each report within the dataset included crucial information such as patient characteristics (age and gender), indication for treatment, reporting year, reporting region, and the outcome of the adverse event.

Statistical Analysis

Descriptive statistics was employed to summarize the clinical characteristics of all cases. For the analysis of categorical variables, we utilized the Chi-square test or Fisher exact test, while the comparison of continuous variables between fatal and non-fatal cases was conducted using the Mann-Whitney test or Student’s t test. A significance level of $P < 0.05$ was considered statistically significant. Logistic regression analysis was performed to elucidate the factors (gender, age at onset, reporting year, reporting region) related to fatal outcomes. Disproportionality analysis, which is widely used in pharmacovigilance study. Safety signals were identified during the analysis of a pharmacovigilance database when an AE was reported more frequently in association with a specific drug compared to all other drugs, or a specified drug (such as cyclosporine), in the database. To calculate this proportionality, reporting odds ratio (ROR) and the information component (IC) were used. A signal was deemed present if both ROR and IC met certain criteria, including a case number of at least 3 and a lower limit of the 95% confidence interval (CI) > 1 for ROR, as well as an IC > 0 and a lower limit of the 95% CI > 0 for IC. Subgroup analysis were conducted based on gender and age. All analyses were conducted using R version 4.2.1.

Results

Descriptive Analysis

In our study, we conducted an analysis of a total of 1,30,157 adverse event cases associated with CNIs from the FAERS database. The data spanned from the Q1 of 2004 to the Q3 of 2023. Within this dataset, our focus was on 221 reports specifically linked to acute pancreatitis. Table 1 provides a summary of the clinical characteristics of these acute pancreatitis cases associated with CNI. The occurrence of CNI-related acute pancreatitis cases was predominantly observed in males (54.95%), with a median age of 43 (IQR: 21–58). The reporting of cases increased over time, reaching a peak in recent years, and was predominantly concentrated in Tacrolimus-related acute pancreatitis cases. Cyclosporine-related acute pancreatitis cases showed a relatively stable reporting frequency. Regarding the geographic distribution of reported cases, the majority were concentrated in Europe (40.27%), followed by Asia (32.58%), and America (21.27%). The outcomes of CNI-related acute pancreatitis were generally serious. The most commonly reported outcome events included hospitalization (38.01%), followed by death (31.67%), other serious outcomes (22.62%), and life-threatening outcomes (7.69%).

Signal Values Associated With CNIs

The frequency of acute pancreatitis associated with CNIs was found to be significantly higher compared to all other drugs in the database, with a ROR of 1.82 (95% CI: 1.60–2.08) and an IC of 0.85 (95% CI: 0.65–1.04), as depicted in Table 2. To further investigate the association between different CNI regimens and acute pancreatitis, we analyzed the risk of acute pancreatitis associated with various CNIs. The analysis revealed that tacrolimus and cyclosporine both carry a risk of inducing acute pancreatitis. When comparing the risk signals for acute pancreatitis between tacrolimus and cyclosporine, the signal for tacrolimus appears to be higher than that for cyclosporine, but the results from two calculation methods are inconsistent (ROR 1.34 [1.02, 1.76], IC 0.16 [-0.15 to 0.47], Table 2).

We simultaneously analyzed the concomitant adverse reactions in these patients. Other concomitant adverse reactions were less frequent, with the top 5 rankings as follows: abdominal pain (19 cases, 8.60%), disseminated intravascular coagulation (15 cases, 6.79%), anemia (14 cases, 6.33%), and respiratory failure (14 cases, 6.33%).

Analysis of Fatal and Non-Fatal Cases

Among cases of CNIs-related acute pancreatitis, the mortality rate was found to be 31.67% (70/221 cases). To investigate the risk factors

Table 1
Characteristics of Patients with CNI Related Acute Pancreatitis Sourced From FAERS Database.

Characteristics	Total Cases (n = 221)	Tacrolimus (n = 141)	Cyclosporine (n = 80)
Gender			
Female	73(33.03)	48(34.04)	25(31.25)
Male	121(54.95)	77(54.61)	44(55.00)
Unknown	27(12.22)	16(11.35)	11(13.75)
Age at onset (years old)			
Median(IQR)	43(21,58)	43(28,58)	42(16,58)
<20	46(20.81)	25(17.73)	21(26.25)
20–39	33(14.93)	27(19.15)	6(7.50)
40–59	64(28.96)	45(31.91)	19(23.75)
≥60	43(19.46)	29(20.57)	14(17.50)
Unknown	35(15.84)	15(10.64)	20(25.00)
Reporting year			
2004–2008	23(10.41)	6(4.26)	17(21.25)
2009–2013	39(17.65)	12(8.51)	19(23.75)
2014–2018	75(33.94)	49(34.75)	18(22.50)
2019–2023(Q3)	108(48.87)	74(52.48)	26(32.50)
Reporting region			
Europe	89(40.27)	60(42.55)	29(36.25)
Asia	72(32.58)	39(27.66)	33(41.25)
America	47(21.27)	38(26.95)	9(11.25)
Oceania	2(0.90)	2(1.42)	0(0.00)
Unknown	11(4.98)	2(1.42)	9(12.25)
Outcomes			
Hospitalization	84(38.01)	53(37.59)	31(38.75)
Death	70(31.67)	47(33.33)	23(28.75)
Other serious	50(22.62)	31(21.99)	19(23.75)
Life-threatening	17(7.69)	10(7.09)	7(8.75)

CNI = calcineurin inhibitors, N = number, IQR = Interquartile range.

Table 2
Signal Value of CNIs With Acute Pancreatitis.

CNIs	N	ROR	95%CI	IC	95%CI
All	221	1.82	1.60, 2.08	0.85	0.65, 1.04
Tacrolimus	141	1.98	1.68, 2.34	0.97	0.72, 1.21
Cyclosporine	80	1.47	1.18, 1.83	0.54	0.22, 0.86
Tacrolimus vs Cyclosporine	-	1.34	1.02, 1.76	0.16	-0.15, 0.47

N = number; ROR = reporting odds ratio; IC = information component; 95%CI = 95% confidence interval.

associated with fatal outcomes in patients experiencing acute pancreatitis, a logistic regression analysis was conducted using available factors in the database. The results of the analysis revealed that as age increases, the risk of adverse reactions in pancreatitis also rises. A lower age serves as a protective factor for death caused by CNIs-related acute pancreatitis (OR 0.943, 95% CI 0.915–0.972, $P = 0.000$, Table 3).

Signal Values Associated With Different Groups of Cases

We conducted an analysis on various subgroups, considering gender and age, to explore the relationship between CNIs and acute pancreatitis. The risk signal for tacrolimus-induced acute pancreatitis was observed in all age and gender groups, except for those over 60 years old. However, the risk signal for cyclosporine-induced acute pancreatitis was present only in the male group (ROR 1.70[1.26–2.28], CI 0.73[0.29–1.17], Figure 1) and the age group <20 years (ROR 2.25[1.46–3.48], CI 1.07[0.43–1.71], Figure 1).

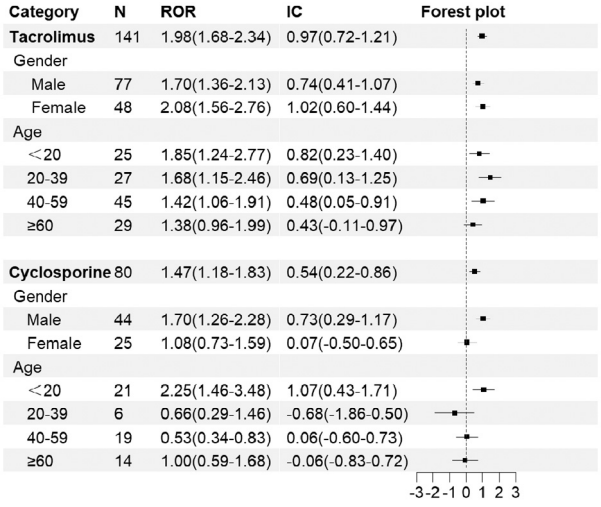

Figure 1. Signal value of CNIs induced acute pancreatitis among gender and age groups (N = number; ROR = reporting odds ratio; IC = information component).

Discussion

Drug-induced acute pancreatitis (DIAP) is recognized as a rare etiology of acute pancreatitis, constituting approximately 0.1–5% of all AP cases.[8–10] Its mechanism is commonly linked to immune mediation.[11] The World Health Organization database has identified over 500 drugs capable of inducing DIAP, with at least 30 directly linked to the onset of AP.[12] Common culprits include tetracyclines, isoniazid, macrolides, metronidazole, and angiotensin-converting enzyme inhibitors.[13] Recent studies have suggested that azathioprine, atorvastatin, and hydrochlorothiazide are frequently associated with hospitalizations due to DIAP.[10] However, scant reports exist regarding the potential of tacrolimus to induce acute pancreatitis. Our research, grounded in the analysis of the FAERS database, seeks to examine the risk of acute pancreatitis associated with tacrolimus and cyclosporine. Additionally, we aim to elucidate the clinical characteristics of reported adverse reactions, providing valuable insights for clinical practice. To the best of our knowledge, our study represents the inaugural exploration of the correlation between CNIs, specifically tacrolimus, and acute pancreatitis using the FAERS database.

Our study found that both tacrolimus and cyclosporine were associated with acute pancreatitis compared to all other drugs in the database.

Table 3
Analysis of Factors Influencing Fatal Outcomes in Tacrolimus-Related Acute Pancreatitis.

Characteristics	Total Cases (n = 221)	Fatal Cases (n = 70)	Non-fatal Cases (n = 151)	*P* Value
Gender	0.229			
Female	73(33.03)	39(55.71)	50(33.11)	
Male	121(54.95)	23(32.86)	82(54.30)	
Unknown	27(12.22)	8(11.43)	19(12.58)	
Age at onset (years old)				**0.000**
Median(IQR)	43(21,58)	58(48,65)	41(16,61)	
<20	46(20.81)	1(1.43)	45(29.80)	
20–39	33(14.93)	8(11.43)	25(16.56)	
40–59	64(28.96)	24(34.29)	40(26.49)	
≥60	43(19.46)	25(35.71)	18(11.92)	
Unknown	35(15.84)	12(17.14)	23(15.23)	
Reporting year				0.452
2004–2008	23(10.41)	12(17.14)	11(7.28)	
2009–2013	39(17.65)	4(5.71)	27(17.88)	
2014–2018	75(33.94)	23(32.86)	44(29.14)	
2019–2023(Q3)	108(48.87)	31(44.29)	69(45.70)	
Reporting region				0.703
Europe	89(40.27)	29(41.43)	60(39.74)	
Asia	72(32.58)	12(17.14)	60(39.74)	
America	47(21.27)	24(34.29)	23(15.23)	
Oceania	2(0.90)	0(0.00)	2(1.32)	
Unknown	11(4.98)	5(7.14)	6(3.97)	

CNI = calcineurin inhibitors, N = number, IQR = interquartile range.

When comparing tacrolimus and cyclosporine, the signal for tacrolimus seemed to be higher. Further analysis revealed that, with the exception of patients aged 60 and above, the signal for tacrolimus remained stable, consistently indicating a notable association. In contrast, the signal for cyclosporine was unstable and observed exclusively in the male group and the age group under 20 years. These findings are consistent with previous literature. Few case reports in the literature have documented tacrolimus-induced acute pancreatitis.[4–6] However, as of now, there have been no reported cases of cyclosporine-induced acute pancreatitis.

Our study indicated that the median age of patients experiencing tacrolimus-induced acute pancreatitis was 43 years, and the incidence was higher in males than females. The reported cases have shown a consistent increase over the years, aligning with previous data on drug-induced acute pancreatitis. Niinomi et al. analyzed adverse event reports submitted to the Japanese Adverse Drug Event Report (JADER) database from 2004 to 2017, identifying 3,443 reports associated with drug-induced acute pancreatitis, involving 431 different drugs. Acute pancreatitis was frequently reported in males in their 60s (58.5%), with 19.1% of cases developing within 4 weeks after treatment.[2]

Current case reports suggested that tacrolimus-induced acute pancreatitis was associated with organ transplants, including heart, liver, lung, and kidney transplantation.[1,4,14–16] The mechanisms behind tacrolimus-induced acute pancreatitis may involve immunologic reactions, cell metabolism, and systemic or local infections.[17] Additionally, some studies propose that calcineurin inhibitors may cause hyperlipidemia, with tacrolimus having a lower incidence compared to cyclosporine.[18] Tacrolimus can decrease the activity and plasma concentration of lipoprotein lipase, leading to hypertriglyceridemia—an independent risk factor for acute pancreatitis.[19,20] However, our study data do not strongly support this proposed mechanisms. Among the adverse event reports of tacrolimus-induced pancreatitis in our study, there were relatively few cases with concurrent adverse reactions, and abdominal pain (8.60%) and disseminated intravascular coagulation (6.79%) ranked highest. Cases with concurrent hyperlipidemia were limited. Hence, our study challenges the notion that hyperlipidemia is a mechanism in tacrolimus-induced pancreatitis.

At present, there are no distinctive clinical features that can differentiate DIAP from other etiologies.[17] Therefore, DIAP can be diagnosed during drug administration and the onset of acute pancreatitis, provided that all other potential causes are excluded. In clinical practice, if a patient develops acute pancreatitis after taking tacrolimus, vigilance should be exercised for the occurrence of drug-related adverse reactions after ruling out other reasons. Research indicates that approximately 40.6% of drug-induced AP occurs within 4 weeks after treatment.[2] In most case reports, patients presented with elevated blood tacrolimus trough levels.[21] Once clarified, timely discontinuation of tacrolimus is recommended. In previous case reports, when tacrolimus was switched to cyclosporine, most patients showed significant improvement in their condition, with relief of abdominal symptoms.[1,17] Therefore, if acute pancreatitis is associated with tacrolimus, switching to cyclosporine could be a beneficial intervention.

Our study is based on a real-world analysis of the FAERS database. Despite the considerable sample size, certain limitations should be acknowledged. Firstly, FAERS relies on spontaneous and voluntary reports, making it susceptible to false reports, underreporting, selective reporting, and incomplete reporting of adverse events. These inherent limitations could introduce bias into the study results. Secondly, while disproportionality analysis is a valuable tool for quantifying signals of AEs, it does not provide information on the incidence rates of both drugs and adverse reactions. Thirdly, we conducted logistic regression based on existing data to analyze risk factors associated with fatal outcomes. However, due to the limited data available in the database, not all relevant factors could be included in the analysis. Therefore, our study can only provide reference based on existing factors and does not constitute an in-depth analysis of risk factors. This limitation constrains our understanding of the true occurrence of adverse reactions.

Conclusion

Our study has identified a safety signal for tacrolimus in relation to acute pancreatitis when compared to all other drugs in the database. Additionally, we observed advanced age as a significant risk factor for tacrolimus-related acute pancreatitis, leading to mortality. Given the widespread use of tacrolimus, it is crucial for healthcare providers to be vigilant and informed about the potential association with acute pancreatitis. Further investigations are warranted to validate and quantify the risk of tacrolimus-induced acute pancreatitis.

Declaration of competing interest

None declared.

Acknowledgments

H. Yang was responsible for study conceptualization and design, data acquisition, data analysis and interpretation, manuscript preparation, manuscript editing; Z.L. An were responsible for study conceptualization; Y. Zhao and H.Z. Lu were responsible for study conceptualization, design, interpretation and manuscript editing.

Ethical Statement

Since the FAERS database is accessible to the public and patient records are anonymized and de-identified, ethical clearance and informed consent are not required for this study.

Data Availability

The datasets presented in this study can be found in the FAERS database https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2024.04.005.

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