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Differential profiles of adverse events associated with mycophenolate mofetil between adult and pediatric renal transplant patients

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Abstract

Objective: Immunosuppressive regimens after renal transplantation usually include a combination of calcineurin inhibitors, corticosteroids, and a proliferation inhibitor, either azathioprine or mycophenolate mofetil (MMF), to prevent rejection and maintain graft function. MMF has a stronger immunosuppressive effect than does azathioprine. This study aimed to examine MMF-associated adverse events in renal transplant patients.

Methods: Retrospective pharmacovigilance disproportionality analysis was conducted using the Japanese Adverse Drug Event Report database.

Results: A total of 11,594 adverse drug events were reported in renal transplant patients; 10,272 (88.6%) involved adults and 1322 (11.4%) involved children. In adult patients, the most frequent adverse events induced by MMF were cytomegalovirus infection (272 reports), urinary tract infection (69 reports), and polyomavirus-associated nephropathy (61 reports). Among adverse events, the highest reporting odds ratio (ROR) was found for cytomegalovirus infection (ROR, 1.58; 95% confidence interval, 1.36–1.83). In pediatric patients, the rank order for MMF-associated adverse events was cytomegalovirus infection (27 reports), bronchitis (23 reports), and cytomegalovirus viremia (19 reports), but these adverse events were not detected as a signal.

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Conclusion: Our results show the safety profile of MMF in pediatric renal transplant patients. These findings can be used to update information used for prescriptions for pediatric patients.

Keywords
Renal transplantation, mycophenolate mofetil, pharmacovigilance analysis, adverse events, reporting odds ratio, cytomegalovirus

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Abbreviations

CI, confidence interval; ROR, reporting odds ratio.

Introduction

Mycophenolate mofetil (MMF), an immunosuppressive drug, is extensively used after renal transplantation.[1] MMF is used in combination with other immunosuppressant medications, mainly with the calcineurin inhibitors cyclosporine and tacrolimus.[2] MMF is also used in the treatment of autoimmune and chronic inflammatory diseases.[3] Early clinical trials have shown that MMF reduces acute rejection in renal transplant patients by 20% to 40% compared with azathioprine, and reduces graft loss and chronic allograft dysfunction.[4–7] However, MMF has been reported to be associated with a high incidence of adverse events.[8–10] In the clinical setting, dose reduction or discontinuation of MMF is often required to alleviate adverse events. This results in an unnecessarily increased risk of acute rejection[11] and poor long-term graft survival.[12]

Recently, there has been growing opinion that detailed evaluation of information gained through pharmacovigilance activity is important for all drugs to ensure their safe use.[13,14] Pharmacovigilance practices can improve the quality of information, which is provided to medical staff and patients in a timely manner, thereby reducing the overall risk to patients. Drugs are approved for clinical use on the basis of showing a satisfactory balance of benefits and risks. However, the safety profile of drugs can change over time because their use expands with the patients' characteristics and the number of patients exposed. In Japan, the "Risk Management Plan Guidance"[15] issued in 2012, describes the basic ideas needed to develop a drug risk management plan, including safety considerations, a drug safety monitoring plan, and a risk minimization plan based on the International Conference on Harmonization E2E guidelines (2004).[16]

This study aimed to obtain a comprehensive, nationwide overview of adverse events associated with MMF in patients with a renal transplantation using an adverse drug events database in Japan composed of voluntarily submitted reports.

Methods

The present study used data that were made available through the public release of the Pharmaceuticals and Medical Devices Agency's Japanese Adverse Drug Event Report (JADER) database. This database contains information on adverse events associated with medications and patients in Japan since April 2004. We used data

from the JADER database between April 2004 and January 2017. The data structure of JADER consists of four data sets as follows: patients' demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history (HISTO). In the REAC table, the Medical Dictionary for Regulatory Activities is used to codify the adverse events, which are indicated as "preferred term".

After we removed duplicated data from the DRUG and REAC tables, the DEMO table was then matched with the REAC and DRUG tables using the ID number. In each case, the medication associated with the adverse event was classified into three categories: "suspected medicine," "concomitant medicine," and "interaction." A suspected medicine is defined as a pharmaceutical product with which an adverse event is suspected to be associated. When the reporter suspects an interaction, he/she reports it as an interaction. A concomitant medicine is defined as other pharmaceutical products that are used at the time of the appearance of an adverse event. We only extracted cases that were classified as suspected medicine, and cases in which drugs were applied to renal transplantation. In the DEMO table, the demographic information table includes age in 10-year intervals, such as 20 to 29 years. In this study, we defined "under 10s" or "10s" as pediatric patients, and defined "20s," "30s," "40s," "50s," "60s," "70s," "80s," "90s", or "100s" as adult patients. There were other codes for age classification, such as "first trimester," "second trimester," "third trimester," "newborn," "infant," "pediatric," "youth," "adult," "elderly," and "unknown." Therefore, we included the codes of "infant," "pediatric," and "youth" in pediatric patients, and included "adult" and "elderly" in adult patients. We analyzed combinations of suspected medicine and adverse events. We compiled a cross-tabulation table on the basis of two classifications: the presence or absence of the adverse event, and the presence or absence of the suspected medicine. Then, we calculated the reporting odds ratio (ROR). The ROR is the probability of reporting one specific adverse event versus all other adverse events for a particular drug and for all other drugs present in the database. A signal was considered when the lower limit of the 95% confidence interval (CI) of the ROR was greater than 1.

Data on age, height, and weight in this database are not provided as continuous variables, but are indicated in the form of age in decades, height in centimeter-denominated ranges, and weight in kilogram-denominated ranges, respectively. Therefore, we could not conduct multiple analyses using these data. All analyses were performed with JMP Pro 12 (SAS Institute Inc. Cary, NC, USA).

Results

A total of 5,195,890 reports (men: 63.2%) were obtained after combination of the three DRUG (2,850,470 reports), REAC (709,826 reports), and DEMO (449,558 patients) tables, using the ID number. Of these, we extracted drugs that were suspected of causing all adverse events (1,984,122 reports) and obtained 11,920 combinations (1,899 patients) of suspected drugs and all adverse events in patients with renal transplantation. Furthermore, reports without information on age (320 reports) and involving neonates (six reports) were excluded. Therefore, a total of 11,594 reports, which consisted of 764 different adverse events (1,808 patients), were obtained. Of these, we stratified data by age corresponding to our definition (adult or pediatric), and 10,272 reports in adult renal transplant patients and 1,322 reports in pediatric renal transplant patients were obtained.

A total of 720 different adverse events were detected in adult renal transplant patients. Of these, 330 different adverse events were associated with MMF as the suspected drug, and were ranked in order of the frequency of reporting (Table 1). The 10 most common adverse events were cytomegalovirus infection, urinary tract infection, polyomavirus-associated nephropathy, cytomegalovirus viremia, pneumonia, *Pneumocystis jirovecii* pneumonia, cytomegalovirus-positive, herpes zoster, diabetes, and impaired renal function. Among these 10 adverse events, a signal was detected for three, namely cytomegalovirus infection (ROR, 1.58; 95% CI, 1.36–1.83), polyomavirus-associated nephropathy (ROR, 2.02; 95% CI, 1.50–2.72), and cytomegalovirus-positive (ROR, 1.81; 95% CI, 1.23–2.68).

For pediatric renal transplant patients, 129 different adverse events were detected. Of those, 55 different adverse events were associated with MMF as the suspected drug, and were ranked in order of the frequency of reporting (Table 2). There was no significant ROR (no signal was detected) among the 10 most common adverse events of cytomegalovirus infection, bronchitis, cytomegalovirus viremia, pneumonia, hypertension, heart failure, hypotension, lymphoproliferative disorder after transplantation, acidosis, and hypoferric anemia.

Table 1. Adverse events of mycophenolate mofetil ranked in order of frequency of reporting among 330 different adverse events in adult renal transplant patients.

	n	ROR (95% CI)
Cytomegalovirus infection	272	1.58 (1.36–1.83)*
Urinary tract infection	69	1.11 (0.85–1.45)
Polyomavirus-associated nephropathy	61	2.02 (1.50–2.72)*
Cytomegalovirus viremia	41	1.31 (0.92–1.84)
Pneumonia	49	1.24 (0.90–1.69)
Pneumocystis jirovecii pneumonia	40	1.24 (0.87–1.75)
Cytomegalovirus-positive	34	1.81 (1.23–2.68)*
Herpes zoster	32	1.31 (0.88–1.93)
Diabetes	29	0.51 (0.35–0.75)
Impaired renal function	23	0.84 (0.54–1.31)

CI, confidence interval; ROR, reporting odds ratio; n, the number of co-occurrences.
*Signal detected (see the Methods section for the criteria of detection).

Discussion

In a large, nationwide survey using pharmacovigilance data, we obtained a comprehensive overview of the adverse events associated with MMF as the suspected causative drug in adult and pediatric renal transplant patients. Of the 720 different adverse events that were recorded on the use of all drugs in adult renal transplantation, 330 (45.8%) were associated with MMF. Similarly, of the 129 different adverse events recorded on the use of all drugs in pediatric renal transplantation, 55 (42.6%) were associated with MMF. Interestingly, differential aspects of frequently occurring adverse events between adult and pediatric renal transplant patients

Table 2. Adverse events of mycophenolate mofetil ranked in order of frequency of reporting among 55 different adverse events in pediatric renal transplant patients.

	n	ROR (95% CI)
Cytomegalovirus infection	27	1.36 (0.87–2.14)
Bronchitis	23	1.43 (0.89–2.31)
Cytomegalovirus viremia	19	1.31 (0.78–2.2)
Pneumonia	7	1.76 (0.76–4.1)
Hypertension	6	0.67 (0.28–1.57)
Heart failure	6	1.19 (0.49–2.88)
Hypotension	5	1.95 (0.71–5.32)

CI, confidence interval; ROR, reporting odds ratio; n, the number of co-occurrences.
*Signal detected (see the Methods section for the criteria of detection).

were observed. Cytomegalovirus infection, polyomavirus-associated nephropathy, and cytomegalovirus-positive were significantly detected in adult renal transplant patients, whereas significant adverse events were not found in pediatric renal transplant patients. To the best of our knowledge, the present survey is the first to demonstrate the safety of MMF, especially in pediatric renal transplant patients.

The JADER database covers several million case reports on adverse events, and submission is voluntary. Pharmacovigilance aims to search for previously unknown patterns and detect important drug-associated adverse events. In Japan, this technique showed various adverse events associated with pregabalin in patients with cancer.[17] Using the US FDA Adverse Event Reporting System, pharmacovigilance analysis identified serious adverse events in patients with organ transplants.[18] In this study, cytomegalovirus infection, cytomegalovirus-positive, and polyomavirus-associated nephropathy were MMF-associated adverse events in adult renal transplant patients. However, no signals were detected as MMF-associated adverse events in pediatric renal transplant patients, partly because of the small size of the pediatric sample. Although our results are in line with the results of clinical studies on cytomegalovirus infection,[19,20] they are inconsistent with the results of a large-scale clinical study on polyomavirus-nephropathy.[21] In this previous clinical study, polyomavirus-nephropathy showed a low incidence ($n = 1$) in pediatric renal transplant patients, despite the fact that MMF was completely discontinued in 13/70 (19%) patients because of adverse effects. Polyomavirus-associated nephropathy is a major reason for graft loss in renal transplant patients.[22] Notably, there is no antiviral treatment available for polyomavirus-nephropathy. Generally, increasing polyoma BK virus loads in plasma results in subsequent reduction in immunosuppression. Therefore, caution is required in adult renal transplant patients.

In our study, some other adverse events associated with MMF in renal transplant patients were detected. Hematological adverse events, such as pancytopenia (11 reports in adult and pediatric patients) and leukocytopenia (11 reports in adult and pediatric patients), and gastrointestinal events (e.g., diarrhea, 22 reports in adult and pediatric patients) were observed. We also found that adverse events, such as hypotension, hypertension, and heart failure were attributed to MMF in pediatric patients. The underlying mechanism for these occurrences is unclear. Therefore, further studies are required to examine their mechanism.

MMF is an inactive prodrug, and after its oral administration, it is extensively absorbed and metabolized to active mycophenolic acid by esterase.[23] Mycophenolic acid shows pharmacological effects,[24] but it is associated with some adverse events. Notably, the concentration of mycophenolic acid is correlated with hematologic disorders, but its association with infection and gastrointestinal disorders is weak.[25] Therefore, predicting the occurrence of infection using therapeutic drug monitoring is difficult.

The JADER database is considered a useful tool, but there are several limitations inherent to voluntary reporting. First, the JADER database has various biases, such as the lack of a denominator that indicates the total number of patients who received the drugs of interest, as well as missing data and confounding factors. Second, the ROR does not provide a robust indication of signal strength. In this type of study, the ROR corresponds to the risk of spontaneous notification of an adverse event and not the risk of adverse event occurrence per se. Finally, the present method did not provide detailed clinical information on the

patients' clinical status (e.g., comorbidities and kidney function before the start of treatment). Because clinically unstable patients are more likely to develop adverse events and take several concomitant drugs than stable patients, this may be a confounding factor in the occurrence of adverse events.

In conclusion, we conducted a comprehensive assessment of the association of MMF with adverse events in renal transplant patients using the JADER database. Our results show the safety profile of MMF in pediatric renal transplant patients. These findings can be used to update information used for prescriptions for pediatric patients.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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