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REVIEW ARTICLE

Exposure-Toxicity Relationships of Mycophenolic Acid in Adult Kidney Transplant Patients

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Abstract

Mycophenolic acid is commonly prescribed in adult kidney transplant recipients for preventing graft rejection. A therapeutic target for total mycophenolic acid area under the concentration–time curve (30–60 mg h/L) has been established in adult kidney transplant recipients and widely referenced today. However, this specific target range does not adequately characterize mycophenolic acid-associated adverse effects. The primary objective of this qualitative and critical review was to characterize the exposure-toxicity relationships of mycophenolic acid in an attempt to determine whether exposure thresholds can be identified. The secondary objective was to determine the associations of clinical variables with specific adverse effects. The inclusion criteria consisted of all peer-reviewed papers in adult kidney transplant subjects (average study age > 18 years) with both exposure (area under the concentration–time curve) and toxicity data. The exclusion criteria were papers involving the pediatric population, studies lacking either area under the concentration–time curve or toxicity data, or studies with no apparent reported variations in area under the concentration–time curves. Of the 28 papers identified, inconsistent findings have been reported for the most frequently characterized adverse events of mycophenolic acid (gastrointestinal, infectious, and hematological), while promising exposure thresholds (i.e., > 40–60 mg h/L for total mycophenolic acid) have been suggested by a few studies. The roles of free mycophenolic acid exposure, mycophenolic acid metabolites, or clinical factors influencing the manifestation of the toxicities also remain to be clarified. Although it is not yet possible to define toxicity threshold(s) for the purpose of mycophenolic acid therapeutic drug monitoring, the information obtained and the limitations identified in this comprehensive literature body have provided a good foundation for future investigations.

Introduction

Mycophenolic acid (MPA) is commonly prescribed in combination with a calcineurin inhibitor and a corticosteroid in adult kidney transplant recipients as part of maintenance immunosuppression therapy for preventing graft rejection [1, 2]. Mycophenolic acid exerts its pharmacological action by inhibiting inosine-5′-monophosphate dehydrogenase, thereby reducing the production of guanosine nucleotides in both B and T lymphocytes [2]. The pharmacokinetics of MPA is highly variable between and within individuals, as evident by up to ten-fold variations often reported in the clinic. Sources of pharmacokinetic variability may involve absorption (e.g., formulation and gastric pH fluctuations), distribution (e.g., free fraction and enterohepatic

Key Points

Gastrointestinal, infectious, and hematological adverse events are frequently associated with mycophenolate in adult kidney transplant recipients; however, the overall collective data are inconclusive to support a consistent relationship between mycophenolate exposure and the manifestation of these adverse events

While promising exposure thresholds (i.e., > 40–60 mg h/L for total mycophenolate) can be hypothesized for the development of toxicity, further investigations using properly powered, controlled, randomized, or blinded trials with the primary aim to investigate specific toxicities are required

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recirculation), metabolism (e.g., genetic polymorphisms in UGT-glucuronosyltransferases and transporters [e.g., multidrug resistance-associated protein 2, solute carrier organic anion transporter family enzymes]), and excretion (e.g. renal function) [1, 3, 4]. Because of the large apparent pharmacokinetic variability, therapeutic drug monitoring of MPA has been recommended by many clinicians to optimize efficacy (e.g., [5]) and minimize toxicity (e.g., [6]). Moreover, the significant plasma protein binding of MPA leading to a low free fraction (1–3% under normal conditions) and the extensive metabolism of MPA in the production of glucuronidated metabolites can further complicate the therapeutic drug monitoring of MPA [1, 3]. These characteristics underscore the importance of considering free MPA concentrations and MPA metabolism while interpreting its pharmacokinetic–pharmacodynamic relationships.

Although there are both proponents and opponents to MPA therapeutic drug monitoring [2], a therapeutic target for the MPA area under the concentration–time curve (AUC; 30–60 mg h/L) has been established in adult kidney transplant recipients and widely referenced today. This specific target range was initially established in a patient population administered mycophenolate mofetil, cyclosporine, and corticosteroids where a significant correlation between total MPA exposure and biopsy-proven acute rejection was evident within 6 months post-transplant [5]. Moreover, it was determined that more subjects with lower MPA exposure (27.6 ± 12.3 mg h/L) had a biopsy-proven acute rejection (27.5%, $n = 51$) compared with sub-groups with higher MPA exposures (54.8 ± 15.3 mg h/L, 14.9%, $n = 47$; or 96.7 ± 32.2 mg h/L, 11.5%, $n = 52$) [5]. The resulting lower threshold of MPA (i.e., 30 mg h/L) for establishing efficacy has been subsequently verified in many other studies [4], supporting a robust pharmacokinetic–pharmacodynamic relationship. However, trends toward higher incidences of adverse events (e.g., gastrointestinal [GI] or hematological) in the high MPA exposure target group in comparison to those with lower exposures were observed in the same study, but the differences were not statistically significant and meaningful thresholds for toxicity were not established [5]. Therefore, this specific MPA upper therapeutic target (60 mg h/L) does not adequately characterize MPA-associated adverse effects and should not be interpreted as the threshold for the development of toxicity.

Mycophenolic acid is associated with many adverse effects [1, 3]. The most common side effects are GI in nature, manifesting in the clinic as nausea, vomiting, stomach cramps, and sometimes bothersome diarrhea [7, 8], which can significantly affect quality of life and lead to high rates of mycophenolate discontinuation [9]. Clinical management of GI side effects usually involves reducing the dose, increasing the dosing frequency, or switching to a potentially gastro-protective enteric-coated formulation to mitigate the hypothesized localized insult to GI mucosa by mycophenolate mofetil [7, 8]. However, complicated side effects such as infections or hematological complications (anemia, leukopenia, neutropenia) can also occur relatively frequently but require more resources for management. More importantly, these severe complications may lead to unwanted complications that may threaten graft survival and significantly reduce the patient's quality of life. For example, a common clinical approach in the absence of MPA exposure data in a neutropenic/leukopenic patient is the empiric reduction of MPA dosage [7, 8], which can result in an increased incidence of graft rejection [10]. A leukopenic patient with infection is also more likely to be admitted to the hospital, requiring significant expenditures in human (nursing, clinical pharmacy) and drug (e.g., broad-spectrum antibiotics, granulocyte-colony stimulating factor) resources. Having clinical tools (i.e., therapeutic thresholds) that can assist clinicians identify the likelihood of developing MPA-associated toxicity would help mitigate these complications and reduce costs associated with their care.

The exposure-toxicity relationships of MPA have been summarized in the solid organ transplant population (e.g., [1, 3]), but a focused and updated critical summary in the adult kidney transplant population is warranted. As it is widely accepted that MPA exposure (i.e., AUC) but not individual concentrations (e.g., trough) best correlates with efficacy and potentially toxicity [4], this review focuses only on exposure data. Furthermore, because of significant differences in pharmacokinetic characteristics in pediatric subjects [11], only adult data, where the majority of the information is available, are presented. The primary objective of this review was to characterize the exposure-toxicity relationships of MPA for individual MPA-associated adverse effects in an attempt to determine whether an exposure threshold can be identified. The secondary objective was to determine the associations of clinical variables (e.g., patient demographical information, type of graft) with specific adverse effects.

2 Data Selection

This was a qualitative and critical review of the peer-evaluated literature. PubMed, MEDLINE, and EMBASE were searched, with no time limits, using combinations of the following terms: mycophenolic acid, mycophenolate, Cellcept, Myfortic, pharmacokinetics, pharmacodynamics, exposure, toxicity, adverse effects, gastrointestinal, hematologic, infection, anemia, leukopenia, neutropenia, and kidney transplant. The reference sections of all identified papers were further screened manually. The inclusion criteria consisted of all papers in adult kidney transplant subjects (average study age > 18 years) with both exposure (AUC) and toxicity data. The exclusion criteria were papers involving the

pediatric population, studies lacking either AUC or toxicity data, or studies with no apparent reported variations in AUCs. All included studies are summarized chronologically in Table 1, incorporating information on the patient population, experimental design, dosing, analytical assay, and exposure-toxicity relationships. For the text discussion, data are presented based on adverse-effect categories: GI, infections, and hematological.

3 Important Mycophenolic Acid-Associated Adverse Events

3.1 Gastrointestinal Adverse Effects

Of the 28 identified papers, 21 have characterized GI adverse events either independently or as a composite of adverse outcomes (Table 1). The most common adverse events characterized were diarrhea, abdominal pain, constipation, dyspepsia, flatulence, nausea, and vomiting. The frequencies of GI side effects are highly variable between and within studies (Table 1). Overall, the relationships between independently characterized GI side effects and MPA exposures have proven to be mixed, with only a limited number of studies supporting an association. In a double-blinded, concentration-controlled study with primarily Caucasian subjects taking mycophenolate mofetil, van Gelder et al. [5] reported trends toward higher incidences of diarrhea (19.2%), vomiting (9.6%), and abdominal pain (13.5%) in their high MPA exposure group (AUC 96.7 ± 32.2 mg h/L) compared with other subjects with lower MPA AUCs (medium 54.8 ± 15.3 mg h/L or low exposure 27.6 ± 12.3 mg h/L) within 6 months of transplant. Despite not reaching statistical thresholds, these findings seemed to suggest an exposure-dependent effect, especially in the case of diarrhea where the incidence increased more than two fold (from 8.5% to 19.2%) with an increase in exposure between the two AUC groups (Table 1). Likewise, in a German population taking enteric-coated mycophenolate, Sommerer et al. [12] reported higher MPA AUCs in individuals with GI side effects ($n = 6$, AUC of 51 mg h/L) compared with subjects with no GI adverse events (AUC of 38 mg h/L) within 2 months post-transplant; however, a subsequent multiple regression analysis failed to identify MPA AUC as a predictor of GI effects. The findings from these two studies suggested that an AUC of 50–60 mg h/L might be the threshold limit for the escalation of diarrhea, but additional analysis (i.e., using receiver-operating characteristic curve) is needed to confirm this hypothesis.

However, in contrast to the findings of van Gelder et al. [5] and Sommerer et al. [12], an inverse relationship has also been reported between MPA exposure and GI toxicity. This was evident in a Japanese population where Kagaya et al. [13] reported a higher number of subjects with diarrhea (56%) had lower MPA AUCs (on day 28) than subjects with elevated MPA AUCs, although no statistical analyses were provided. Similarly, in a retrospective study by Pillans et al. [14] in a Caucasian cohort, GI adverse events were found in subjects with reduced exposure ($n = 4$, AUC 23.7 ± 2.43 mg h/L, days 2–5) compared with individuals with no documented GI events ($n = 23$, AUC 33.2 ± 1.73 mg h/L) (Table 1). This observation may be explained by the direct insult of MPA or its metabolites on luminal surfaces of the GI tract (i.e., the lower the absorption, the higher the local concentration) or an artefact of not capturing MPA exposure at the same time as the occurrence of GI side effects, which may explain the apparent inverse association between systemic exposure and toxicity.

Further support for an exposure-GI toxicity relationship was not evident in other studies using mycophenolate mofetil in primarily Caucasian populations. Atcheson et al. [15] did not find an association between MPA AUC (measured on day 5) and the occurrence of GI events within 1 month post-transplant. In a randomized controlled study, active MPA concentration adjustment led to increased MPA AUC on day 14 (33.7 vs. 27.1 mg h/L, respectively) and day 30 (45.0 vs. 30.9 mg h/L) post-transplant compared with a fixed-dosing regimen, but the higher exposure did not translate to increased GI events (97% vs. 90%, respectively) within 12 months of follow-up [16]. In an extended-duration (5 years) observational study [6], the proportion of subjects with non-infectious diarrhea was similar in patients with an AUC < 30 mg h/L (5.8%) compared with those with an AUC of 30–60 mg h/L (3.9%) or an AUC > 60 mg h/L (4.4%). In patients subjected to intensified MPA dosing for the first 5 days [17], increased MPA AUC on day 3 (59.3 mg h/L vs. 40.3 mg h/L standard dosing) and day 5 (59.3 mg h/L vs. 46.8 mg h/L) did not translate to increased incidence of constipation (35.3% vs. 29.9%), diarrhea (51.5% vs. 41.8%), dyspepsia (13.2% vs. 19.4%), nausea (50% vs. 49.3%), or vomiting (22.1% vs. 28.4%) during the 6 months of follow-up. Lack of differences in the incidence of GI effects between the two groups was further confirmed in a categorical analysis using an MPA AUC cut-off of 60 mg h/L determined at 5 days post-transplant [17]. Furthermore, in patients with early corticosteroid withdrawal, Le Meur et al. [18] also did not observe a difference in the overall incidence of diarrhea between the concentration-control (15%) or fixed-dosing (8.8%) groups over 12 months, despite significantly higher MPA AUCs at week 2 (36.2 ± 14.8 mg h/L vs. 29.3 ± 12.4 mg h/L, respectively) and week 6 (44.2 ± 16.1 mg h/L vs. 36.8 ± 18.1 mg h/L) post-transplant (Table 1). Finally, in a Chinese cohort, concentration control of MPA led to reduced MPA AUC (54.06 mg h/L, day 30) compared with fixed dosing (61.38 mg h/L), but this did not translate to differences in diarrhea occurrence (19.8% vs. 22%, respectively] over the 12-month follow-up period [19] (Table 1).

Table 1 Summary of study findings on MPA exposure-toxicity relationships in adult kidney transplant recipients

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 141 **Type of graft:** cadaveric **Ethnicity:** 140 Caucasian **Age (years):** 47.8 ± 11.5 (low dose), 46.9 ± 13.8 (intermediate), 50.6 ± 10.5 (high) **Sex:** 58.8–63.8% male **Weight (kg):** 69.8 ± 12.5 (low dose), 65.9 ± 13.1 (intermediate), 67.4 ± 11.3 (high) **Renal function:** serum creatinine 1.66 mg/dL (low dose), 1.47 mg/dL (intermediate), and 1.31 mg/dL (high) **Post-Tx time:** within 6 months	Prospective, double blind, concentration-controlled	**Induction:** NA **Maintenance MMF/day:** 0.9–4.23 g per treatment group **Co-medication:** cyclosporine (dose variable) and prednisone (dose not specified)	HPLC, total concentration; metabolite data not available	AUC (week 20, via limited sampling approach): ≥ 1 adverse event: 81% in high exposure group ($n = 52$, AUC at week 20 of 96.7 ± 32.2 mg h/L) vs. 77% in intermediate group ($n = 47$, AUC at week 20 of 54.8 ± 15.3 mg h/L) vs. 74% in the low exposure group ($n = 51$, AUC at week 20 of 27.6 ± 12.3 mg h/L) ($p > 0.05$). Note: adverse events not characterized at the same time as AUC measurement **GI:** Diarrhea: 19.2% (high) vs. 8.5% (intermediate) vs. 7.8% (low) ($p > 0.05$) Vomiting: 9.6% (high) vs. 6.4% (intermediate) vs. 2% (low) ($p > 0.05$) Abdominal pain: 13.5% (high) vs. 8.5% (intermediate) vs. 5.9% (low) ($p > 0.05$) **Infections:** Pneumonia: 3.8% (high) vs. 6.4% (intermediate) vs. 5.9% (low) ($p > 0.05$) **Hematological effects:** Leukopenia: 21.2% (high) vs. 12.8% (intermediate) vs. 11.8% (low) ($p > 0.05$)	van Gelder 1999 [5]
Sample size: 31 **Type of graft:** 28 cadaveric **Ethnicity:** NA **Age (years):** 43 (16–67) **Sex:** 17 men **Weight (kg):** NA **Renal function:** 59 mL/min (23–78) on day 8 **Post-Tx time:** up to 3 months	Prospective, open-label, observational	**Induction:** anti-thymocyte globulin 4 mg/kg/day × 10 days **Maintenance MMF/day:** 2 g but adjusted based on tolerance **Co-medication:** cyclosporine (5–10 mg/kg/day) and corticosteroids (tapered to 5 mg daily by 3 months)	EMIT, total concentration, metabolite not available	AUC_{0-12} (early post transplant and up until 3 months post transplantation): Composite of adverse events (leukopenia, anemia, diarrhea, esophagitis, thrombocytopenia) ($n = 11$, AUC of 66.82 ± 29.87 mg h/L) vs. no adverse events ($n = 12$, 55.70 ± 11.74 mg h/L) for patients remaining on 1 g twice daily regimen ($p > 0.05$)	Mourad 2001 [34]
Sample size: 51 **Type of graft:** cadaveric **Ethnicity:** NA **Age (years):** 49 (32–68) **Sex:** 29 men **Weight (kg):** NA **Renal function:** 47.5 mL/min (22.7–81) on day 8 **Post-Tx time:** up to 3 months	Prospective, open-label, observational	**Induction:** NA **Maintenance MMF/day:** 1 g but adjusted based on tolerance **Co-medication:** tacrolimus (0.2 mg/kg/day with dose adjustment) and corticosteroids (tapered to 10 mg daily by 3 months)	EMIT, total concentration, metabolite not available	AUC_{0-12} (early post transplant and up until 3 months post transplantation): Composite of adverse events (leukopenia, anemia, diarrhea, esophagitis, thrombocytopenia) ($n = 31$ sample profiles, AUC of 48.38 ± 18.50 mg h/L) vs. no adverse events ($n = 47$, 36.04 ± 10.82 mg h/L) for patients remaining on 0.5 g twice daily regimen ($p < 0.05$). Receiver operating characteristic analysis indicated an AUC cut-off of 37.6 mg h/L (sensitivity 83.3%, specificity 59.6%) for threshold of toxicity	Mourad 2001 [33]
Sample size: 27 **Type of graft:** 33% living donor **Ethnicity:** Caucasian **Age (years):** 39 (21–65) **Sex:** 78% male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 1 month	Retrospective	**Induction:** NA **Maintenance MMF/day:** 2 g **Co-medication:** cyclosporine (dose variable) and prednisone (0.3 mg/kg)	HPLC, total concentration, metabolite not available	AUC (days 2–5, via limited sampling approach): **GI:** GI adverse event ($n = 4$, AUC 23.7 ± 2.43 mg h/L) vs. no GI adverse event ($n = 23$, AUC 33.2 ± 1.73 mg h/L) ($p < 0.05$)	Pillans 2001 [14]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 39 **Type of graft:** cadaveric **Ethnicity:** NA **Age (years):** 49.4 ± 13.1 **Sex:** 19 male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 months	Prospective, single-blinded, observational	**Induction:** daclizumab 1 mg/kg × 5 **Maintenance MMF/day:** 2 g **Co-medication:** tacrolimus (0.2 mg/kg/day with dose adjustment) and methylprednisolone (12 mg, tapered off over 5 months)	HPLC, total and free MPA concentrations, metabolite data available	AUC_{0-12} (at the time of adverse effect [within 7 days]): **Hematological effects:** Within the same subjects, no difference in total MPA AUC, free MPA AUC, MPA glucuronide AUC, or MPA acyl-glucuronide AUC during occurrence of anemia ($n = 29$) and leukopenia ($n = 12$) vs. periods of no adverse effects Between subjects, leukopenic patients ($n = 10$, MPA glucuronide AUC 1312 mg h/L) vs. normal subjects (AUC 920 mg h/L) ($p = 0.05$) Between subjects, anemic patients ($n = 19$, MPA glucuronide AUC 1022 mg h/L) vs. normal subjects (AUC 799 mg h/L) ($p = 0.06$)	Kuypers 2003 [35]
Sample size: 100 **Type of graft:** cadaveric **Ethnicity:** NA **Age (years):** 51.4 ± 13.8 **Sex:** 59 men **Weight (kg):** 67.2–70.1 **Renal function:** creatinine clearance 36.9–51.9 mL/min **Post-Tx time:** 12 months	Prospective, single-blinded, observational	**Induction:** daclizumab 2 mg/kg ×1, then 1 mg/kg × 4 ($n = 31$) **Maintenance MMF/day:** 1 to 2 g **Co-medication:** tacrolimus (0.2 mg/kg/day with dose adjustment) and methylprednisolone (12–20 mg, tapered off over 5 months or maintained at 4 mg)	EMIT, total concentration, metabolite not available	AUC_{0-12} (7 [full AUC], 42, 90, and 360 days post-transplant) with limited sampling approach: **Infections:** Infections ($n = 5$–17) vs. no infection ($n = 78$–85) have similar AUC over the entire study period ($p > 0.05$) **Hematological effects:** Leukopenia ($n = 11$, AUC 61.4 ± 30.9 mg h/L) vs. no leukopenia ($n = 81$, AUC 42.3 ± 25.3 mg h/L) at 3 months post transplant ($p < 0.05$) Leukopenia ($n = 5$, AUC 84.4 ± 45.6 mg h/L) vs. no leukopenia ($n = 75$, AUC 44.2 ± 21.9 mg h/L) at 12 months post transplant ($p < 0.05$) Anemia ($n = 51$, AUC 49.4 ± 28.9 mg h/L) vs. no anemia ($n = 38$, AUC 37.5 ± 19.4 mg h/L) at 3 months post transplant ($p < 0.05$) Anemia ($n = 21$, AUC 61.1 ± 31.9 mg h/L) vs. no anemia ($n = 62$, AUC 42.3 ± 21.3 mg h/L) at 12 months post transplant ($p < 0.05$)	Kuypers 2004 [29]
Sample size: 42 **Type of graft:** 31% living **Ethnicity:** 98% Caucasian **Age (years):** 44.3 ± 13.1 **Sex:** 57% male **Weight (kg):** 72.9 ± 14.8 **Renal function:** creatinine clearance 40.1 ± 22 mL/min **Post-Tx time:** within 1 month	Prospective, open-label, observational	**Induction:** basiliximab 20 mg day 0 and 4, **Maintenance MMF/day:** 2 g **Co-medication:** cyclosporine 4 mg/kg twice daily ($n = 32$) or tacrolimus 0.1 mg/kg twice daily with dose adjustment ($n = 10$); prednisolone 0.3 mg/kg daily; diltiazem 240 mg daily	HPLC for total concentration; MS for free concentrations	AUC_{0-6} (day 5, via limited sampling approach) **GI:** GI adverse event ($n = 4$) vs. no GI adverse event (AUC data not available) ($p > 0.05$) **Infection or hematological effects:** Thrombocytopenia or leukopenia or infection (MPA AUCfree 1.9 ± 0.3 mg h/L) vs. no adverse effects (MPA AUCfree 1.1 ± 0.1 mg h/L) ($p < 0.05$). Note: no difference observed using total AUC	Atcheson 2004 [15]
Sample size: 46 **Type of graft:** 97% living donor **Ethnicity:** Japanese **Age (years):** 38 ± 14 **Sex:** NA **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 2 weeks	Prospective, open-label, observational	**Induction:** 37% used "an antibody to interleukin-2-receptor" **Maintenance MMF/day:** 1252 ± 30.7 mg **Co-medication:** 52% with cyclosporine (dose not specified), 48% (dose not specified) with tacrolimus, steroid not specified	EMIT; total concentration; metabolite data not available	Overall, AUC_{0-9}: adverse effect group (composite of CMV ($n = 12$), varicella ($n = 2$), and GI ($n = 1$)) of 39.2 ± 22.8 mg h/L vs. no adverse event ($n = 21$): 30.1 ± 8.0 mg h/L ($p > 0.05$) Cyclosporine subgroup, AUC_{0-9}: Adverse effect group ($n = 10$) of 30.0 ± 10.0 mg h/L vs. no adverse event ($n = 18$) of 29.6 ± 8.3 mg h/L ($p > 0.05$) Tacrolimus subgroup, AUC_{0-9}: Adverse effect group ($n = 5$) of 55.7 ± 31.1 mg h/L vs. no adverse event ($n = 3$) of 32.6 ± 6.7 mg h/L ($p > 0.05$)	Okamoto 2005 [31]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 21 **Type of graft:** NA **Ethnicity:** Japanese **Age (years):** 39.7 **Sex:** 9 male **Weight (kg):** 56 **Renal function:** NA **Post-Tx time:** 28 days after transplantation	Retrospective	**Induction:** NA **Maintenance MMF/day:** 2 g but adjusted based on tolerance **Co-medication:** tacrolimus (0.15 mg/kg, adjusted based on concentration) and corticosteroids (tapered to 10 mg daily by week 4)	HPLC, total concentration, metabolite not available	AUC_{0-12} (day 28): **Infections:** Viral infections including CMV, varicella zoster virus, adenovirus hemorrhagic cystitis, and malignancy related to Epstein-Barr virus ($n=5$, AUC of 61.5 ± 30.3 mg h/L) vs. no viral infections ($n=16$, 50.4 ± 31.6 mg h/L) ($p > 0.05$).	Satoh 2005 [32]
Sample size: 290 (total) **Type of graft:** NA **Ethnicity:** 87.5–92.6% Caucasian **Age (years):** ~52 **Sex:** 52–68% **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 months	Prospective, open-label, randomized, controlled	**Induction:** monoclonal antibody against IL-2 receptor or antibodies against T-cells **Maintenance MMF/day:** fixed-dose arm 2 g × 4 weeks; dose in concentration-control arm titrated to target **Co-medication:** cyclosporine (titrated to target) or tacrolimus (titrated to target) and corticosteroids (regimen not specified)	HPLC and MS, total concentration, metabolites available	Sub-study of the FDCC trial [38] AUC (day 3, day 10, month 1, 3, 6, and 12) using abbreviated methods for MPA or trapezoidal rule for metabolites **GI:** Numerical AUC data not provided. No differences in MPA AUC values in patients with (24%) or without diarrhea No difference in Acyl MPA glucuronide AUC_{0-2} or MPA glucuronide AUC_{0-2} in patients with or without diarrhea	Heller 2007 [25]
Sample size: 137 (total)—70 in concentration-control group (A) and 67 in fixed-dose group (B) **Type of graft:** NA **Ethnicity: Caucasian** (French) **Age (years):** ~50 in both groups **Sex:** 71% (group A) and 58% (group B) male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 months **PRA:** 0% for majority of subjects	Prospective, open-label, randomized, controlled	**Induction:** basiliximab 20 mg on days 0 and 4 **Maintenance MMF/day:** 2 g in the fixed-dose group and variable dose in the concentration-control group **Co-medication:** cyclosporine (titrated based on targets) and prednisone (tapered off in 4–6 months)	Type of assay not specified, total concentration; metabolite data not available	Median AUC_{0-12} (day 7, day 14, month 1, 3, 6, and 12) using population-based, Bayesian-abbreviated methods Day 7 (24.7 mg h/L vs. 25.4 mg h/L, concentration-controlled vs. fixed-dose), day 14 (33.7 mg h/L vs. 27.1 mg h/L, $p < 0.05$), month 1 (45.0 mg h/L vs. 30.9 mg h/L, $p < 0.05$), month 3 (43.6 mg h/L vs. 37.5 mg h/L), month 6 (37.2 mg h/L vs. 33.1 mg h/L), and month 12 (36.8 mg h/L vs. 42.0 mg h/L) No difference between two groups with respect to occurrence of **GI:** GI events (97% vs. 90%, concentration-controlled vs. fixed-dose), **Infections:** Overall infection (77% vs. 74%), CMV infection (32% vs. 32%), bacterial infection (45% vs. 43%) **Hematological effects:** Anemia (66% vs. 61%), leukopenia (40% vs. 34%), 8 cases of herpes infection in concentration-controlled group vs 1 case in fixed-dose group ($p < 0.05$)	Le Meur 2007 [16]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 100 **Type of graft:** 98% cadaveric **Ethnicity:** Caucasian **Age (years):** 51.4 ± 13.8 **Sex:** 59 men **Weight (kg):** 67.2–74.4 (day 7–year 5) **Renal function:** creatinine clearance 36.8–55.7 mL/min (day 7–year 5) **Post-Tx time:** 5 years	Prospective, open-label, single-blinded (to pharmacokinetic data), observational	**Induction:** NA **Maintenance MMF/day:** 1–2 g **Co-medication:** tacrolimus (dose titrated to target) and methylprednisolone ("low dose", tapered over time)	EMIT; total concentration; metabolite data not available	AUC (day 7, week 6, month 3, year 1, 3, and 5) using abbreviated methods for MPA (except for day 7 which utilized full curve) Timing of AUC and adverse event pre-determined: within 7 days of day 7 AUC, within 2 weeks of 6-week and 3-month AUC, with 4 weeks of 6 month AUC, and "time preceding" years 1,3,5 AUCs **GI:** Proportion of subjects with non-infectious diarrhea: AUC < 30 mg h/L (5.8%) vs. AUC 30–60 mg h/L (3.9%) vs. AUC > 60 mg h/L (4.4%) ($p > 0.05$) **Infections:** Proportion of subjects with infections: AUC < 30 mg h/L (9.9%) vs. AUC 30–60 mg h/L (10%) vs. AUC > 60 mg h/L (7.1%) ($p > 0.05$) **Hematological effects:** Proportion of subjects with leukopenia: AUC < 30 mg h/L (5%) vs. AUC 30–60 mg h/L (7%) vs. AUC > 60 mg h/L (12.4%) ($p < 0.05$) Proportion of subjects with anemia < 12 g/L/d: AUC < 30 mg h/L (40.8%) vs. AUC 30–60 mg h/L (52.2%) vs. AUC > 60 mg h/L (64.3%) ($p < 0.05$) Proportion of subjects with anemia < 10 g/L/d: AUC < 30 mg h/L (14.2%) vs. AUC 30–60 mg h/L (17%) vs. AUC > 60 mg h/L (25%) ($p < 0.05$)	Kuypers 2008 [6]
Sample size: 71 **Type of graft:** Living **Ethnicity:** Japanese **Age (years):** 42.9 ± 11.9 **Sex:** 36 male **Weight (kg):** 55.9 ± 12.8 **Renal function:** serum creatinine 4.2 ± 0.4 g/dL **Post-Tx time:** 28 days	Prospective, open-label, observational	**Induction:** NA **Maintenance MMF/day:** 1–2 g **Co-medication:** tacrolimus (dose titrated to target) and prednisone (tapering dose, to 10 mg by week 4)	HPLC, total concentration, metabolite data not available	AUC_{0-12} (day 28): **GI:** Proportion of subjects with diarrhea: MPA AUC < 50 mg h/L (56%) vs. AUC 50–70 mg h/L (19%) vs. AUC 70–100 mg h/L (19%), vs. AUC 100–140 mg h/L (25%), vs. AUC ≥ 140 mg h/L (14%) (no statistical analysis)	Kagaya 2008 [13]
Sample size: 332 **Type of graft:** NA **Ethnicity:** 88% Caucasian **Age (years):** 48.7 ± 12.8 **Sex:** 62% male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 months	Prospective, open-label, randomized, controlled	**Induction:** "induction therapy allowed" **Maintenance MMF/day:** fixed-dose arm 2 g × 4 weeks; dose in concentration-control arm titrated to target **Co-medication:** cyclosporine (titrated to target) or tacrolimus (titrated to target) and corticosteroids (regimen not specified)	HPLC and MS, total concentration, metabolites available	Sub-study of the FDCC trial [38] AUC (day 3, day 10, month 1, 3, 6, and 12) using abbreviated methods for MPA. Method for metabolite AUC not specified **GI:** 28/218 subjects with acyl MPA glucuronide concentration developed diarrhea within 1 month. 19% in TAC-treated group developed diarrhea vs. 9.8% in CsA group (3–12 months post-transplant). Other rates not available No difference in Acyl MPA glucuronide AUC (at day 3 or month 3) in patients with [2.45 mg h/L, day 3] or without [1.93 mg h/L, day 3] diarrhea (in the first month or between 3–12 months, respectively) **Hematological effects:** 16.1% ($n = 22$) of subjects developed leukopenia between 3–12 months in TAC treated group. Low event rate in CsA group. No difference in Acyl MPA glucuronide AUC (at month 3) in patients with [1.36 mg h/L] or without [1.15 mg h/L] leukopenia (between 3–12 months post-transplant) in the TAC treated group	van Agteren 2008 [26]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 720 (total) – 243 (concentration-control with reduced CNI, group A), 237 (concentration-control with normal CNI, group B), 240 (fixed-dose with standard CNI, group C) **Type of graft:** cadaveric 49% (group A), 49.8% (group B), 51.7% (group C) **Ethnicity:** Caucasian 65.8% (group A), 70.9% (group B), and 69.6% (group C) **Age (years):** 48.3 (group A), 48.8 (group B), 49.6 (group C) **Sex:** ~ 32% male in all groups **Weight (kg):** N/A **Renal function:** baseline glomerular filtration ~ 65–67 mL/min across groups **Post-Tx time:** 12 months	Prospective, open-label, randomized, controlled	**Induction:** mixture of antithymocyte globulin, basiliximab, and daclizumab **Maintenance MMF/day:** dose titrated in groups A&B. **Co-medication:** cyclosporine or tacrolimus (dose titrated to targets) and prednisone (dose not specified)	Type of assay not specified, total concentration; metabolite data not available	AUC_{0-12} (day 10, month 1, 3, 6, and 12) using abbreviated methods Day 10 AUC: 31.7 ± 14.7 and 38.9 ± 15.0 mg h/L (CsA and TAC, Group A) vs. 30.4 ± 12.3 and 38.5 ± 13.9 mg h/L (CsA and TAC, Group B) vs. 30.0 ± 11.3 and 38.2 ± 15.4 mg h/L (CsA and TAC, Group C) (no statistics between same CNI regimen between groups) 1 month AUC: 39.2 ± 15.7 and 46.1 ± 16.0 mg h/L (CsA and TAC, Group A) vs. 32.3 ± 13.1 and 46.4 ± 17.0 mg h/L (CsA and TAC, Group B) vs. 36.3 ± 14.1 and 45.8 ± 15.5 mg h/L (CsA and TAC, Group C) (no statistics between same CNI regimen between groups) 3 month AUC:40.1 ± 19.7 and 48.3 ± 18.9 mg h/L (CsA and TAC, Group A) vs. 41.4 ± 16.9 and 49.4 ± 18.7 mg h/L (CsA and TAC, Group B) vs. 36.1 ± 11.3 and 49.2 ± 20.2 mg h/L (CsA and TAC, Group C) (no statistics between same CNI regimen between groups) 6 month AUC:48.8 ± 25.1 and 47.4 ± 17.2 mg h/L (CsA and TAC, Group A) vs. 43.9 ± 16.6 and 47.0 ± 19.5 mg h/L (CsA and TAC, Group B) vs. 34.6 ± 15.5 and 46.2 ± 17.7 mg h/L (CsA and TAC, Group C) (no statistics between same CNI regimen between groups) 12 month AUC:46.0 ± 14.1 and 47.9 ± 17.0 mg h/L (CsA and TAC, Group A) vs. 46.1 ± 19.2 and 45.3 ± 18.3 mg h/L (CsA and TAC, Group B) vs. 39.1 ± 14.3 and 48.8 ± 19.0 mg h/L (CsA and TAC, Group C) (no statistics between same CNI regimen between groups) No differences between groups with respect to occurrence of the following: **GI:** Diarrhea (Group A: CsA 13%, TAC 47%; Group B: CsA 36%, TAC 46%; Group C: CsA 14%, TAC 46%) **Infections:** Opportunistic infections (Group A: CsA 13%, TAC 9%; Group B: CsA 16%, TAC 12%; Group C: CsA 7%, TAC 11%) **Hematological effects:** Leukopenia (Group A: CsA 18%, TAC 25%; Group B: CsA 27%, TAC 26%; Group C: CsA 26%, TAC 30%) **Others:** Hypertension (Group A: CsA 18%, TAC 24%; Group B: CsA 18%, TAC 23%; Group C: CsA 26%, TAC 20%) Diabetes (Group A: CsA 5%, TAC 16%; Group B: CsA 4%, TAC 12%; Group C: CsA 2%, TAC 9%) Malignancies (Group A: CsA 5%, TAC 2%; Group B: CsA 0%, TAC 3%; Group C: CsA 2%, TAC 3%)	Gaston 2009 [30]
Sample size: 66 **Type of graft:** 42.4% living **Ethnicity:** Caucasian (German) **Age (years):** 41 (19–68) **Sex:** 32 male **Weight (kg):** NA **Renal function:** glomerular filtration 46 (30–76) mL/min **Post-Tx time:** 10–56 days	Prospective, open-label, observational	**Induction:** basiliximab on days 0 and 4 **Maintenance enteric-coated mycophenolate/day:** 720 to 2440 mg **Co-medication:** cyclosporine (100–300 mg twice daily) and methylprednisolone (12–20 mg daily)	EMIT; total concentration; metabolite data not available	AUC_{0-12} (timing not specified): **GI:** GI side effects ($n = 6$, AUC of 51 mg h/L [29–76], median[range]) vs. no side effect (AUC of 38 mg h/L [7–130]) ($p < 0.05$) **Infections:** Infections ($n = 9$, AUC of 65 mg h/L [37–130], median[range]) vs. no infection (AUC of 37 mg h/L [7–120]) ($p < 0.05$). In multiple regression analyses, MPA AUC_{0-12} was the only variable predicting infections ($R = 0.44$, SE = 0.32). MPA AUC did not predict gastrointestinal adverse effects.	Sommerer 2010 [12]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 75 (total) **Type of graft:** 27% living **Ethnicity:** 74 Caucasian (German) **Age (years):** 49.9 ± 14.5 **Sex:** 53% male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 3 months	Prospective, open-label, randomized, parallel-groups	**Induction:** basiliximab 20 mg on days 0 and 4 **Maintenance Enteric-Coated mycophenolate/day:** standard (1440 mg) or intensified (2880 mg for 15 days, then 2160 mg until day 42, then 1440 mg) **Co-medication:** cyclosporine (dose titrated to target) and methylprednisolone (tapering dose to 4 mg daily until end of study)	HPLC, total concentration, free fraction, metabolites available	AUC_{0-12} (time with respect to adverse events not specified): Day 3 AUC:45 ± 15.70 mg h/L (intense) vs. 32.60 ± 18.71 mg h/L (standard) ($p < 0.05$) Day 10 AUC: 42.80 ± 17.40 mg h/L(intense) vs. 31.30 ± 18.40 mg h/L (standard) ($p < 0.05$) Day 21 AUC: 41.60 ± 17.20 mg h/L (intense) vs. 31.60 ± 15.80 mg h/L (standard) ($p < 0.05$) **GI, infections, or hematological effects:** No difference between intensified vs. standard regimens with respect to hematological disorders (6 vs. 5%), GI disorders (18 vs. 14%), or infections (14 vs.15%)	Glander 2010 [20]
Sample size: 135 (total) – 68 (intense group) vs. 67 (standard) **Type of graft:** deceased in 56% (intense) vs. 63% (standard) **Ethnicity:** 82.4% (intense) vs. 79.1% (standard) Caucasian **Age (years):** 44.4 ± 12.4 (intense) vs. 47.5 ± 13.2 (standard) **Sex:** 69.1% (intense) vs. 67.2% (standard) male **Weight (kg):** ~ 77–78 kg **Renal function:** ~ 55 mL/min at 6 months **Post-Tx time:** within 6 months	Prospective, open-label, randomized, controlled	**Induction:** IL-2 antibody (82–89%) **Maintenance MMF/day:** intensified 3 g on days 1–5, then 2 g daily) or standard (2 g/day) **Co-medication:** tacrolimus (dose titrated to 8–15 ng/mL) and prednisone (per specific center practice)	HPLC, total concentration, metabolite not available	AUC_{0-12} (days 3 and 5 post-transplant) and limited sampling schedule-generated AUC at discharge and on months 1 and 3 Day 3 AUC: 59.3 mg h/L (intense) vs. 40.3 mg h/L (standard) ($p < 0.05$) Day 5 AUC: 59.3 mg h/L (intense) vs. 46.8 mg h/L (standard) ($p < 0.05$) No differences in other AUC readings No difference between intensified vs. standard regimens with respect to the following: **GI:** Constipation (35.3 vs. 29.9%), diarrhea (51.5 vs. 41.8%), dyspepsia (13.2 vs. 19.4%), nausea (50 vs. 49.3%), vomiting (22.1 vs. 28.4%), and weight loss (1.5 vs. 1.5%) **Infections:** CMV infection (1.5 vs. 9.0%), herpes simplex (10.3 vs. 9%), and urinary tract infection (16.2 vs. 25.4%) **Hematological effects:** Anemia (42.6 vs. 38.8%), leukopenia (14.7 vs. 22.4%), neutropenia (5.9 vs. 3%), and thrombocytopenia (2.9 vs. 3%) Anemia more frequent in individuals with MPA AUC > 60 mg h/L at day 5 ($n = 38$, 55.3%) vs. MPA AUC ≤ 60 mg h/L at day 5 (35%, $n = 80$) **Others:** Diabetes (13.2 vs. 16.4%) and tremor (30.9 vs. 37.3%), No difference between individuals with MPA AUC ≤ 60 mg h/L vs. MPA AUC > 60 mg h/L at day 5 with respect to leukopenia (20 vs. 18.4%), neutropenia (5.0 vs. 5.3%), thrombocytopenia (3.8 vs. 2.6%), constipation (32.5 vs. 23.7%), diarrhea (51.3 vs. 44.7%), dyspepsia (20.0 vs. 13.2%), nausea (48.8 vs. 50.0%), vomiting (21.3 vs. 34.2%), weight loss (0 vs. 2%), diabetes (20 vs. 5.3%), tremor (38.8 vs. 29%), CMV infection (7.5 vs. 0%), herpes simplex (8.8 vs. 10.5%), and urinary tract infection (21.3 vs. 18.4%)	Gourishankar 2010 [17]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 441 (total) – intensified 218 (PK sample = 41), standard 223 (PK sample = 44) **Type of graft:** cadaveric 59.2% (intensified) vs. 65.9% (standard) **Ethnicity:** Caucasian 87.6% (intensified) vs. 82.1% (standard) **Age (years):** ~ 46 **Sex:** ~ 62% male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 6 months	Prospective, open-label, randomized, parallel-groups	**Induction:** 75% received induction therapy (not specified) **Maintenance enteric-coated mycophenolate/day:** same as Glander 2010 [20] **Co-medication:** cyclosporine (titrated to target) and corticosteroids (tapered to 5 mg/day throughout study)	HPLC or MS, total concentration, metabolite not available	Part of the data from Sommerer 2011 and Glander 2010 [20, 39] Median AUC_{0-12} (up until 87 days-post transplant): AUC 33% to 47% higher in intensified group vs. standard group in the first 6 weeks post-transplant Total # adverse events in intensified (98.6%) vs. standard (97.3%) regimens ($p > 0.05$) Total # of severe adverse events (55.4% vs. 49.8%) ($p > 0.05$) Malignancy (2.8% vs. 2.3%) ($p > 0.05$) Adverse events causing discontinuation (18.8% vs. 13.2%) ($p > 0.05$) CMV infection (1.9% vs. 0.5%) ($p > 0.05$) Patient with adverse event leading to reduction/interruption (31.5% vs. 20.5%) ($p < 0.05$) Leukopenia (6.6% vs. 4.1%), diarrhea (6.1% vs. 2.3%), CMV (1.9% vs. 0.5%) ($p > 0.05$) **GI:** Total # GI adverse events (77% vs. 70.3%) ($p > 0.05$) Serious GI adverse events (8.9% vs. 7.8%) ($p > 0.05$) Abdominal pain (13.1% vs. 9.1%) ($p > 0.05$) Constipation (36.2% vs. 30.1%) ($p > 0.05$) Diarrhea (29.6% vs. 24.2%) ($p > 0.05$) Nausea (31% vs. 26.9%) ($p > 0.05$) Vomiting (22.1% vs. 26.9%) ($p > 0.05$) **Infections:** Total # infections (61.5% vs. 63.5%) ($p > 0.05$) Serious infections (23% vs. 24.2%) ($p > 0.05$) CMV (7.5% vs. 12.8%) ($p > 0.05$) BK virus infection (3.8% vs. 1.8%) ($p > 0.05$) Upper respiratory tract (8% vs. 5.9%) ($p > 0.05$) Urinary tract infection (34.7% vs. 32.9%) ($p > 0.05$) Herpes zoster (2.8% vs. 2.3%) ($p > 0.05$) Pneumonia (3.3% vs. 5%) ($p > 0.05$) Wound infection (3.3% vs. 0.5%) ($p > 0.05$) **Hematological effects:** Total# hematological adverse effects (39.4% vs. 39.3%) ($p > 0.05$) Serious hematological adverse effects (4.2% vs. 0.5%) ($p > 0.05$) Anemia (25.8% vs. 25.1%) ($p > 0.05$) Leukopenia (13.1% vs. 12.3%) ($p > 0.05$) Thrombocytopenia (4.7% vs. 2.7%) ($p > 0.05$) **Others:** Nasopharyngitis (2.8% vs. 2.3%) ($p > 0.05$) Rhinitis (4.2% vs. 4.1%) ($p > 0.05$)	Budde 2011 [21]
Sample size: 247 (total) – concentration control $n = 127$, fixed dose $n = 125$ **Type of graft:** both, % not specified **Ethnicity:** Caucasian (French) **Age (years):** 48.5 ± 13.1 **Sex:** 66.4% male **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 month 0% panel reactive antibody	Prospective, randomized, open-label, controlled	**Induction:** anti-interleukin-2-receptor antibody **Maintenance MMF/day:** fixed dose 2 g/day or concentration control starting with 3 g/day × 10 days followed by AUC target of 40 mg h/L **Co-medication:** cyclosporine (titrated to target) and 7 days of corticosteroids (early withdrawal)	HPLC, total concentration, metabolite not available	AUC_{0-12} (weeks 2, 6, 12, 26, and 52) using population-based, Bayesian-abbreviated methods Week 2 AUC: 36.2 ± 14.8 mg h/L (concentration control) vs. 29.3 ± 12.4 mg h/L (fixed dosing) ($p < 0.05$) Week 6 AUC: 44.2 ± 16.1 mg h/L (concentration control) vs. 36.8 ± 18.1 mg h/L (fixed dosing) ($p < 0.05$) AUC in other time points non-significantly different **GI:** Overall incidence of diarrhea in concentration control (15%) vs. fixed dose group (8.8%) ($p > 0.05$) **Infections:** Overall incidence of bacterial infections in concentration control (48.8%) vs. fixed dose group (44.8%) ($p > 0.05$) Overall incidence of CMV infections in concentration control (24.4%) vs. fixed dose group (16.0%) ($p > 0.05$) Overall incidence of herpes infections in concentration control (7.9%) vs. fixed dose group (4.8%) ($p > 0.05$)	Le Meur 2011 [18]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: Intensified 49, standard 52 **Type of graft:** 74.3% cadaveric (total) **Ethnicity:** 95% Caucasian (total) **Age (years):** 52.4 ± 13.5 **Sex:** 55.4% male **Weight (kg):** NA **Renal function:** glomerular filtration 54.8 mL/min (intensified) vs. 57.6 mL/min **Post-Tx time:** 12 months	Prospective, open-label, randomized, parallel-groups	**Induction:** all on basiliximab **Maintenance enteric-coated mycophenolate/day:** same as Glander 2010 [20] **Co-medication:** cyclosporine (titrated to target) and prednisone ~ 5 mg/day throughout the study	HPLC, total concentration, metabolite data not available	Continuation of the study from Sommerer 2011 and Glander 2010 [20, 39] AUC measurements per Glander 2010 [20, 39] Month 0–12 (intention to treat populations) Overall severe adverse event in intensified (69.8%) vs. standard (64.6%) ($p > 0.05$). This was noted as 69.8% (intensified) vs. 50.5% (standard) in the text with $p < 0.05$ **GI:** GI disorders (82.5% vs. 75.4%) ($p > 0.05$) Abdominal pain (20.6% vs. 9.2%) ($p > 0.05$) Constipation (30.2% vs. 23.1%) ($p > 0.05$) Diarrhea (39.7% vs. 40%) ($p > 0.05$) Dyspepsia (6.3% vs. 0%) ($p > 0.05$) Nausea (36.5% vs. 30.8%) ($p > 0.05$) Vomiting (27% vs. 27.7%) ($p > 0.05$) **Infections:** Infection (73% vs. 80%) ($p > 0.05$) CMV infection (11.1% vs. 13.8%) ($p > 0.05$) BK infection viremia (6.3% vs. 3.1%) ($p > 0.05$) BK nephropathy (0%) Respiratory infection (4.8% vs. 9.2%) ($p > 0.05$) Upper respiratory tract infection (3.2% vs. 1.5%) ($p > 0.05$) Pneumonia (14.3% vs. 12.3%) ($p > 0.05$) Urinary tract infection (46% vs. 47.7%) ($p > 0.05$) **Hematological effects:** Hematological (50.8% vs. 50.8%) ($p > 0.05$) Anemia (28.6% vs. 32.3%) ($p > 0.05$) Leukopenia (25.4% vs. 30.8%) ($p > 0.05$) Thrombocytopenia (6.3% vs. 3.1%) ($p > 0.05$) Month 6–12 (follow-up populations) Overall severe adverse event in intensified (26.5%) vs. standard (15.4%) ($p > 0.05$) **GI:** GI disorders (38.8% vs. 28.8%) ($p > 0.05$) Abdominal pain (0% vs. 1.9%) ($p > 0.05$) Constipation (4.1% vs. 1.9%) ($p > 0.05$) Diarrhea (12.2% vs. 9.6%) ($p > 0.05$) Dyspepsia (2.0% vs. 0%) ($p > 0.05$) Nausea (0% vs. 3.8%) ($p > 0.05$) Vomiting (4.1% vs. 5.8%) ($p > 0.05$) **Infections:** Infection (54.2% vs. 46.2%) ($p > 0.05$) CMV infection (8.2% vs. 1.9%) ($p > 0.05$) BK infection viremia (0% vs. 3.8%) ($p > 0.05$) BK nephropathy (0%) Respiratory infection (4.1% vs. 1.9%) ($p > 0.05$) Upper respiratory tract infection (2.0% vs. 0%) ($p > 0.05$) Pneumonia (6.1% vs. 3.8%) ($p > 0.05$) Urinary tract infection (24.5% vs. 25%) ($p > 0.05$) **Hematological effects:** Hematological (22.4% vs. 28.8%) ($p > 0.05$) Anemia (8.2% vs. 11.5%) ($p > 0.05$) Leukopenia (4.1% vs. 15.4%) ($p > 0.05$) Thrombocytopenia (2% vs. 0%) ($p > 0.05$)	Arns 2013 [22]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 61 **Type of graft:** NA **Ethnicity:** NA **Age (years):** 43 ± 12 **Sex:** 34 men **Weight (kg):** 74.9 ± 16.7 **Renal function:** creatinine clearance 58.4 ± 24.4 mL/min **Post-Tx time:** 4.7 ± 2.9 years	Prospective, open-label, observational	**Induction:** NA **Maintenance MMF/day:** NA **Co-medication:** cyclosporine ($n = 28$, dose not specified) or tacrolimus ($n = 24$, dose not specified) and corticosteroids ($n = 54$, dose not specified)	HPLC, total concentration, metabolite data available	AUC_{0-4} (time with respect to adverse events not specified): **Hematological effects:** Normal hemoglobin ($n = 42$, MPA AUC 26.80 ± 10.27 mg h/L) vs. < normal hemoglobin ($n = 19$, MPA AUC 28.00 ± 13.46 mg h/L) ($p > 0.05$); no correlation between AUC and hemoglobin values Normal hematocrit ($n = 34$, MPA AUC 27.90 ± 10.40 mg h/L) vs. < normal hematocrit ($n = 27$, MPA AUC 26.18 ± 12.34 mg h/L) ($p > 0.05$); no correlation between AUC and hematocrit Normal erythrocytes ($n = 42$, MPA AUC 28.84 ± 11.20 mg h/L) vs. < normal erythrocytes ($n = 19$, MPA AUC 23.23 ± 10.53 mg h/L) ($p > 0.05$); no correlation between AUC and erythrocyte counts No correlations between MPA AUC and leukocytes or platelets Normal hemoglobin ($n = 34$, MPA glucuronide AUC 328.71 ± 178.63 mg h/L) vs. < normal hemoglobin ($n = 17$, MPA glucuronide AUC 639.47 ± 424.25 mg h/L) ($p < 0.05$); significant correlation between AUC and hemoglobin values Normal hematocrit ($n = 30$, MPA glucuronide AUC 387.02 ± 312.98 mg h/L) vs. < hematocrit ($n = 21$, MPA glucuronide AUC 496.97 ± 319.15 mg h/L) ($p > 0.05$); significant correlation between AUC and hematocrit values Normal erythrocytes ($n = 36$, MPA glucuronide AUC 420.60 ± 323.50 mg h/L) vs. < erythrocytes ($n = 15$, MPA glucuronide AUC 460.37 ± 310.24 mg h/L) ($p > 0.05$); no correlation between AUC and erythrocyte counts No correlations between MPA glucuronide AUC and leukocytes or platelets	Sobiak 2013 [37]
Sample size: 240 (96.6% on MMF) **Type of graft:** 92.9% cadaveric **Ethnicity:** NA **Age (years):** 47.1 ± 13.7 **Sex:** 64% men **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 24–60 months 30.8% with panel reactive antibody > 0%	Retrospective	**Induction:** basiliximab or antithymocyte globulin (77.5%) **Maintenance MMF/day:** dose titrated to target (30–60 mg h/L) **Co-medication:** cyclosporine (dose titrated to target) or tacrolimus (dose titrated to target) and corticosteroids (1 mg/kg/day, tapered off over 4 months in low risk patients)	Assay not specified, total concentration, metabolite not available	AUC_{0-12} (at 3 months post-transplant): **Infections:** BK virus viruria mean occurrence 7.6 ± 7.2 months post-transplant; 48% with BK virus, 39% with sustained BK virus, and 27% high-level viruria during study period BK virus viremia mean occurrence 7.9 ± 8.9 months post-transplant; 25% with BK virus, 20% with sustained BK virus, and 7% proven polyomavirus-associated nephropathy Receiver operating characteristic analysis indicated an AUC cut-off of 50 mg h/L (sensitivity 46%, specificity 83%) for threshold of polyomavirus-associated nephropathy MPA AUC > 50 mg h/L associated with viremia and polyomavirus-associated nephropathy ($p < 0.05$), irrespective of type of calcineurin inhibitor used. Various other clinical factors associated with BK virus viremia (including TAC trough)	Borni-Duval 2013 [28]
Sample size: 183 (total)—concentration control $n = 101$, fixed dose $n = 82$ **Type of graft:** living related **Ethnicity:** Chinese **Age (years):** ~ 33 in 2 groups **Sex:** 70.3% male in concentration control; 72% male in fixed dosing **Weight (kg):** NA **Renal function:** NA **Post-Tx time:** 12 months Panel reactive antibody < 10%	Prospective, open-label, observational	**Induction:** NA **Maintenance MMF/day:** fixed dosing 2 g/day × 30 days, then titrated clinically; concentration-control group titrated dose to target MPA AUC 30–60 mg h/L **Co-medication:** tacrolimus (titrated per target) and prednisone (tapering dose until maintenance of 5 mg daily)	Assay not specified, total concentration, metabolite not available	AUC_{0-12} (only day 30 data available for 2 groups) using limited sampling strategies: Concentration control (AUC 54.06 mg h/L) vs. fixed dose (AUC 61.38 mg h/L) ($p < 0.05$) **GI:** Diarrhea in concentration control group (19.8%) vs. fixed dose (22%) ($p > 0.05$) **Infections:** Overall infections in concentration control group (16.8%) vs. fixed dose (31.7%) ($p < 0.05$), but no difference in specific infections (e.g. bacterial, viral, fungal) Majority of infection documented < 6 months post-transplant **Hematological effects:** Anemia in concentration control group (51.5%) vs. fixed dose (56.1%) ($p > 0.05$)	Fu 2014 [19]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: low dose ($n=32$) and standard dose ($n=28$) **Type of graft:** NA **Ethnicity:** Chinese **Age (years):** ~37 in 2 groups **Sex:** ~72% in 2 groups **Weight (kg):** 64-66 kg **Renal function:** glomerular filtration rate 52.4–56.3 mL/min at 6 months **Post-Tx time:** 6 months	Prospective, open-label, randomized, parallel-group	**Induction:** rabbit antihuman thymocyte immunoglobulin **Maintenance enteric-coated mycophenolate/day:** standard group (1440 mg on days 0–30, 1260 mg days 31–60, 1080 mg thereafter) vs. low dose (1080 mg daily) **Co-medication:** tacrolimus (titrated per target) and corticosteroid (prednisone 10 mg daily for 5 days)	EMIT; total concentration; metabolite data not available	AUC_{0-12} (days 3 and 5) using full curve, and abbreviated AUC (2 weeks, months 1, 3, 6) with limited sampling strategies: Day 3 AUC: standard dose (57.4 mg h/L) vs. low dose group (38.2 mg h/L) ($p<0.05$) Day 5 AUC: standard dose (59.3 mg h/L) vs. low dose group (44.8 mg h/L) ($p<0.05$) Week 2: standard dose AUC > low dose group ($p<0.05$) (no numerical values) Months 1 – 6: no differences in AUC between 2 groups No differences in overall or individual adverse events (observed in 6 months) between 2 groups (low dose vs. standard dose) as follows **GI:** GI disorder (43.8% vs. 57.1%) Abdominal pain (18.8 vs. 25%) Constipation (12.5 vs. 14.3%) Diarrhea (25 vs. 32.1%) Dyspepsia (6.3 vs. 10.7%) Flatulence (25 vs. 32.1%) Nausea (18.8 vs. 25%) Vomiting (6.3 vs. 10.7%) **Infections:** Infection (40.6 vs. 42.9%) CMV infection (6.3 vs 10.7%) Respiratory tract infection (12.5 vs. 21.4%) Pneumonia (6.3 vs. 10.7%) Urinary tract infection (31.3 vs. 35.7%) **Hematological effects:** Hematological disorders (46.9 vs. 53.6%) Anemia (25 vs 25%) Leukopenia (18.8 vs. 25%) Thrombocytopenia (9.4 vs. 14.3%) Time of occurrence of adverse events not available	Ding 2014 [23]
Sample size: 67 **Type of graft:** cadaveric **Ethnicity:** 35 African American (AA) and 32 Caucasian (C) **Age (years):** 47.5–50.4 (across groups) **Sex:** 29 females, 38 males **Weight (kg):** 73.1–94.8 (across groups) **Renal function:** glomerular filtration 49.8–64.5 mL/min (across groups) **Post-Tx time:** > 2.56 years post transplant for all groups	Prospective, open-label, observational	**Induction:** NA **Maintenance enteric-coated mycophenolate/day:** empiric dosing adjusted to clinical response **Co-medication:** tacrolimus (titrated to target). Unclear if subjects were on corticosteroids	LCMS, total concentration, metabolite data available	AUC_{0-12} for MPA and MPA glucuronide at time of adverse event **GI:** GI adverse events assessed by validated scale In entire group, no association between MPA or MPA glucuronide AUC and GI adverse events were observed In patients with MPA AUC > 60 mg h/L and GI adverse event, trends of females having higher GI score (3.93 ± 1.71) vs. males (2.67 ± 1.30) evident ($p>0.05$)	Tornatore 2015 [27]

Table 1 (continued)

Patient population	Study design	Dosing regimen	Assay	Exposure—toxicity relationship	References
Sample size: 209 (total)—intensified 82, standard dosing 127 **Type of graft:** cadaveric (donation after circulatory death) **Ethnicity:** Chinese **Age (years):** ~42 (in 2 groups) **Sex:** 53.7% in intensified vs. 52.8% in standard group **Weight (kg):** NA **Renal function:** glomerular filtration ~ 60–63 mL/min 1 month post-transplant **Post-Tx time:** 12 months	Retrospective	**Induction:** antithymocyte globulin or basiliximab **Maintenance enteric-coated mycophenolate/day:** intensified (2160 mg/day for 1 week, then 1440 mg/day for 1 week, then 720–1080 mg/day) vs. standard (1440 mg/day for 1 week, then 1080 mg/day for 1 week, then 720–1080 mg/day) **Co-medication:** tacrolimus (titrated to target) and corticosteroids (tapered to 10 mg within 1st month)	EMIT; total concentration; metabolite data not available	AUC_{0-12} (day 7) using the full curve Intensified group (AUC 66.18 ± 35.48 mg h/L) vs. standard group (45.30 ± 23.5 mg h/L) at day 7 post transplant ($p < 0.05$) 1 week post-op, hemoglobin in intensified group (88.29 g/L) lower than standard group (92.78 g/L) ($p < 0.05$) No statistical differences between the incidence of adverse events between two groups as follows: **GI:** Diarrhea (intense group, 14% vs. standard group, 20%) Intestinal obstruction (1% vs. 3%) **Infections:** Infection (29% vs. 48%) Pulmonary infection (11% vs. 20%) Urinary tract infection (8% vs. 11%) Digestive tract infection (3% vs. 5%) BK virus-associated nephropathy (3% vs. 4%) Peritransplant soft tissue infection (4% vs. 7%) **Hematological effects:** Severe anemia (< 60 g/L) (5% vs. 7%) Severe leukopenia ($< 3 \times 10^9$/L) (6% vs. 8%)	Peng 2018 [24]
Sample size: 21 **Type of graft:** cadaveric and live **Ethnicity:** NA **Age (years):** 56 ± 11 **Sex:** 21 males **Weight (kg):** 76 ± 23 (1 month), 79 ± 25 (6 months), and 79 ± 26 (12 months) **Renal function:** glomerular filtration 54 ± 13 mL/min/1.73 m^2 (1 month), 62 ± 12 (6 months), and 62 ± 11 (12 months) **Post-Tx time:** up to 12 months	Prospective, open-label, observational	**Induction:** NA **Maintenance MMF/day:** 1.9 ± 0.2 g (1 month), 1.5 ± 0.5 g (3 months), and 1.6 ± 0.5 g (12 months) **Co-medication:** tacrolimus (adjusted to target). Corticosteroid-free	LCMS, total concentration, metabolite not available	AUC (1 month, 6 months, and 12 months) using limited sampling approaches **Hematological effects:** Inverse association between MPA AUC/dose (mg h/L/g) and absolute neutrophil count at 1 month ($r^2 = 0.295$, $p < 0.05$), 3 months ($r^2 = 0.661$, $p < 0.05$), and 12 months ($r^2 = 0.682$, $p < 0.05$) based on single linear regression analysis. Similar findings using multiple regression modeling incorporating multiple covariates At 1 month, dose-normalized AUC 53.4 ± 14.5 mg h/L/g in subjects with absolute neutrophil count less than 4.5×10^3 cells/mm^3 vs. 41.2 ± 11.5 mg h/L/g in subjects with absolute neutrophil count greater than $4.5x10^3$ cells/mm^3 ($p < 0.05$) Overall findings remained similar with un-normalized AUC values (numerical data not provided)	Kiang 2018 [36]

AUC: area under the concentration-time curve; CMV: cytomegalovirus infection; CNI: calcineurin inhibitor; CSA: cyclosporine; EMIT: enzyme multiplied immunoassay technique; GI: gastrointestinal; HPLC: high performance liquid chromatography; LCMS: liquid chromatography-mass spectrometry; MMF: mycophenolate; MPA: mycophenolic acid; MS: mass spectrometry; NA: not available or not specified; Tx: transplant; TAC: tacrolimus

The lack of association between MPA exposure and GI toxicity was also observed in studies that have utilized enteric-coated mycophenolate. In a short parallel-controlled study in primarily Caucasian patients, Glander et al. [20] did not observe a difference in GI disorders (18% vs. 14%) despite higher MPA AUCs in the intensified group on day 3 (45 ± 15.70 mg h/L vs. 32.60 ± 18.71 [standard dosing]), day 10 (42.80 ± 17.40 mg h/L vs. 31.30 ± 18.40), and day 21 (41.60 ± 17.20 mg h/L vs. 31.60 ± 15.80) post-transplant. In a similarly designed study with a larger sample size and longer follow-up period of 6 months, Budde et al. [21] also did not draw a relationship between elevated MPA AUCs (week 6) in their intensified MPA dosing group and increased frequencies of total GI adverse events (Table 1). Moreover, the incidence of GI adverse events appeared to occur more frequently within the first 6 months post-transplant, as demonstrated by Arns et al. [22] where relatively fewer events were identified within the follow-up period between 6 and 12 months in comparison to the entire study period from 1 to 12 months. Consistent with other studies, irrespective of the follow-up period, no differences in the incidences of GI adverse events were observed by Arns et al. [22]. Furthermore, negative findings were also observed in Chinese subjects taking enteric-coated mycophenolate, where neither Ding et al. [23] nor Peng et al. [24] reported differences in GI adverse effects (including abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, vomiting) between the intensified dosing group that exhibited higher MPA AUCs (measured at 2 weeks in Ding et al. and day 7 in Peng et al.) and standard dosing groups (Table 1).

In addition to MPA data, attempts to correlate MPA metabolite exposures and GI side effects have not been successful. Heller et al. [25] characterized the exposures of both acyl MPA glucuronide and MPA glucuronide in patients administered mycophenolate mofetil and found no differences in subjects with or without diarrhea. van Agteren et al. [26] also did not report altered AUCs of acyl MPA glucuronide (measured at day 3 or month 3) in relation to episodes of diarrhea reported within the first month or between 3 and 12 months post-transplant. Likewise, in subjects administered enteric-coated mycophenolate, Tornatore et al. [27] found no associations between MPA glucuronide AUC (characterized at time of event) and GI adverse effects. However, the authors did find a trend of female subjects having a higher GI score compared with male patients in a subset of subjects with an AUC > 60 mg h/L, which might indicate a potential sex sensitivity toward these GI adverse events (Table 1).

3.2 Infections

Of the 28 identified papers, 18 have characterized infection events either independently or as a composite of adverse outcomes (Table 1). The most commonly reported events were cytomegalovirus (CMV), BK virus, upper respiratory tract, pneumonia, and urinary tract infections. The frequencies of infections varied significantly between studies (Table 1). Overall, only a limited number ($n = 4$) of studies have supported a relationship between MPA exposure and the occurrence of infections. In a primarily Caucasian population, Atcheson et al. [15] reported higher free MPA exposure (1.9 ± 0.3 mg h/L, measured on day 5) in subjects taking mycophenolate mofetil with a composite of thrombocytopenia, leukopenia, or infection compared with patients exhibiting no adverse effects (free MPA AUC 1.1 ± 0.1 mg h/L) within 1 month of transplant. However, the significance was lost with total MPA AUC and no analysis on infection events itself was conducted. In a German population taking enteric-coated mycophenolate, subjects with infections exhibited higher total MPA AUC (65 mg h/L, timing not specified) compared with those without infections (37 mg h/L) during a follow-up period of 56 days. These findings were supported by further multiple regression analyses where MPA AUC was identified as the only variable capable of predicting infection ($r = 0.44$) [12], although the specific details of the infection events were not available.

Similarly, in a larger study with a longer follow-up period (24–60 months), it was determined that an MPA AUC > 50 mg h/L (measured at 3 months post-transplant) was associated with viremia and polyomavirus-associated nephropathy based on a receiver operating characteristic analysis, although other clinical factors such as tacrolimus concentration also have contributed to BK viremia [28]. In the same study, both BK virus viruria and viremia occurred relatively early ~ 7.6 to 7.9 months post-transplant, with up to 48% of the subjects experiencing an episode of viruria (Table 1). However, because the majority (77.5%) of the patients were administered anti-thymocyte globulin, it was not clear whether this specific induction therapy had a role in enhancing the association or manifestation of this viral infection. Finally, in a Chinese population, Fu et al. [19] reported a lower infection rate in their concentration-control group compared with the fixed-dosing group (16.8% vs. 31.7%) during the 12-month follow-up period. This observation correlated with differences in MPA exposures (i.e., 54.06 mg h/L vs. 61.38 mg h/L) documented in the concentration-controlled vs. fixed-dosing groups, respectively, suggesting an AUC of 60 mg h/L might be the threshold for the escalation of infection events. However, further analyses on specific types of infection (e.g., bacterial, viral, and fungal) did not lead to significant findings between their treatment groups (Table 1). Consistent with the findings of Borni-Duval et al. [28], the majority of infections were also documented within 6 months post-transplant. Taken together, these data provide some evidence supporting an MPA exposure-infection relationship.

In contrast to the aforementioned studies, the majority of the studies ($n = 14$) have not supported an MPA exposure-infection relationship. This is evident in several studies with Caucasian subjects taking mycophenolate mofetil (Table 1). In a double-blinded concentration-controlled study, the incidence of pneumonia (3.8–6.4%) within the 6-month follow-up period was not different between patients with varying MPA AUCs [5]. Throughout a follow-up period of 12 months, patients with documented infection had similar MPA AUCs compared to subjects without active infections [29]. Moreover, active concentration-control of MPA resulted in elevated MPA AUCs early post-transplant but did not translate to increased occurrence of overall infection (77% vs. 74%) [16], CMV (1.5% vs. 9% [17] or 24.4% vs. 16.0% [18]), herpes simplex (10.3% vs. 9% [17] or 7.9% vs. 4.8% [18]), bacterial (48.8% vs. 44.8% [18]), or urinary tract infections (16.2% vs. 25.4%) [17] captured over 6–12 months. In the study by Gourishankar et al. [17], the occurrence of infections was also similar between patients with MPA AUC < 60 mg h/L or AUC > 60 mg h/L. Likewise, over a 5-year follow-up period, the proportion of subjects with infection was similar between patients with AUC < 30 mg h/L (9.9%), AUC 30–60 mg h/L (10%), or AUC > 60 mg h/L (7.1%) when MPA exposure was captured around the time of the event [6]. Finally, in a multi-arm comparative study, the occurrence of opportunistic infections (7–16%) was similar between patients in the MPA concentration-control group (with or without reduced calcineurin inhibitor dosing) compared to fixed MPA dosing, despite apparent differences in MPA exposure [30].

Similar negative findings were evident in subjects taking enteric-coated sodium mycophenolate (Table 1). In a primarily Caucasian population, intensified treatment for 2 weeks resulted in increased MPA AUCs from day 3 to day 21 (31.60 ± 15.80 mg h/L of standard dosing vs. 41.60 ± 17.20 mg h/L), but no differences in the incidence of infections within the 3-month period were observed (14% vs. 15%) [20]. Using a larger sample size over a longer follow-up period, intensified treatment further increased the MPA AUC by 47% by week 6 (vs. standard dosing), but the total number of infections (61.5% vs. 63.5% respectively; including CMV [7.5% vs. 12.8%], BK virus [3.8% vs. 1.8%], upper respiratory tract [8% vs. 5.9%], urinary tract [34.7% vs. 32.9%], herpes zoster [2.8% vs. 2.3%], nasopharyngitis [2.8% vs. 2.3%], or pneumonia [3.3% vs. 5%]) during the 6-month follow-up period remained the same [21]. Moreover, using the same experimental design but extending the follow-up to 12 months, the incidence of overall infection (73% vs. 80%; including CMV [11.1% vs. 13.8%], BK viremia [6.3% vs. 3.1%], respiratory infection [4.8% vs. 9.2%], upper respiratory tract [3.2% vs. 1.5%], pneumonia [14.3% vs. 12.3%], or urinary tract infection [46% vs. 47.7%]) also remained comparable [22]. Consistent with other MPA-associated adverse effects, most infection events were documented within 6 months post-transplant (Table 1).

In Japanese populations taking mycophenolate mofetil, Okamoto et al. [31] found trends of increased MPA AUC (39.2 ± 22.8 mg h/L, $n = 12$) in subjects identified to have adverse effects (composites of CMV infection, varicella infection, and GI side effects) compared with subjects with no side effects (AUC of 30.1 ± 8.0 mg h/L, $n = 21$) over a 2-week observational period. In a subgroup analysis, patients taking tacrolimus exhibiting adverse effects appeared to have further elevated MPA AUCs (55.7 ± 31.1 mg h/L, $n = 5$) compared with subjects without adverse events (32.6 ± 6.7 mg h/L), but none of these differences were statistically significant (Table 1). Similarly, Satoh et al. [32] also reported trends of increased MPA AUCs (61.5 mg h/L, $n = 5$) in Japanese patients with viral infections (i.e., CMV, varicella zoster, adenovirus, and malignancy related to Epstein–Barr virus) compared with patients without viral infections (AUC of 50.4 ± 31.6 mg h/L, $n = 16$) during 28 days post-transplant ($p > 0.05$). The MPA AUC levels were comparable between the two Japanese studies for subjects taking concurrent tacrolimus, and these values were higher than those obtained in subjects taking cyclosporine [31], possibly owing to the inhibitory effects of cyclosporine on the enterohepatic recirculation of mycophenolate. Although MPA exposure can vary significantly based on the co-administered calcineurin inhibitor, it is not clear whether this can lead to different thresholds of toxicities. Similar to the Japanese population, Chinese patients taking enteric-coated mycophenolate receiving intensified dosing had elevated MPA AUCs early post-transplant (e.g., 59.3 mg h/L vs. 44.8 mg h/L [standard dosing] on day 5), but this did not translate to increased infection (40.6% vs. 42.9%, including CMV [6.3% vs. 10.7%], respiratory tract [12.5% vs. 21.4%], pneumonia [6.3% vs. 10.7%], or urinary tract infection [31.3% vs. 35.7%]) over 6 months. These findings were reproduced by Peng et al. [24] in another Chinese cohort where increased AUCs in their intensified treatment group (66.18 ± 35.48 mg h/L vs. 45.30 ± 23.5 mg h/L [standard group] on day 7) also did not translate to increased incidences of infection (29% vs. 48%, including pulmonary [11% vs. 20%], urinary tract [8% vs. 11%], digestive tract [3% vs. 5%], BK virus-associated nephropathy [3% vs. 4%], or soft-tissue infection [4% vs. 7%]) during 12 months post-transplant. Overall, the observation of a lack of association between MPA exposure and infection is consistent between ethnicities.

3.3 Hematological Disorders

Of the 28 identified papers, 19 have characterized hematological side effects either independently or as a composite of adverse outcomes (Table 1). The most commonly reported

events were leukopenia and anemia, with only a limited number of studies investigating neutropenia. The frequencies of hematological disorders varied significantly between studies (Table 1). Similar to the other adverse effects discussed in this paper, only a limited number ($n=6$) of studies have supported a relationship between MPA exposure and the occurrence of hematological toxicities. Inconsistent findings have also been reported from different investigators.

In patients taking a low-dose mycophenolate mofetil regimen co-administered with tacrolimus, Mourad et al. [33] found a significant difference in MPA exposure in subjects presenting with composite adverse events (leukopenia, anemia, diarrhea, esophagitis, thrombocytopenia) [$n=31$ sample profiles, AUC of 48.38 ± 18.50 mg h/L) compared with subjects with no adverse events ($n=47$, 36.04 ± 10.82 mg h/L) during the 3-month follow-up period. A further receiver operating characteristic analysis also indicated an MPA exposure cut-off of 37.6 mg h/L for developing toxicity (Table 1). However, in a similarly designed trial by the same investigators using a higher dose of mycophenolate mofetil co-administered with cyclosporine, the relationships between MPA exposure and the same composite adverse outcomes were lost [34]. Consistent with the occurrence of GI or infectious complications, this observation supports the notion that other clinical factors (e.g., type of concurrent calcineurin inhibitor) should be considered when interpreting the adverse outcomes of MPA. Furthermore, Kuypers et al. [29] reported higher total MPA exposure for subjects with leukopenia compared with those with no leukopenia at 3 months (61.4 ± 30.9 mg h/L vs. 42.3 ± 25.3 mg h/L) or 12 months post-transplant (84.4 ± 45.6 mg h/L vs. 44.2 ± 21.9 mg h/L). Similar associations between MPA exposure and anemia were also observed (Table 1).

However, in a previous study in a much smaller sample ($n=39$), the same authors did not observe statistically significant correlations between total MPA AUC, free MPA AUC, MPA glucuronide AUC, or MPA acyl-glucuronide AUCs with respect to anemia and leukopenia, despite trends indicating higher exposure in patients with documented hematological toxicities [35]. These findings further underscore the importance of a power analysis in these relatively small observational studies. However, Atcheson et al [15] were able to find a relationship between free MPA AUC (characterized on day 5) and either thrombocytopenia or leukopenia within 1 month post-transplant, as evident by patients exhibiting side effects having higher exposure (MPA AUCfree 1.9 ± 0.3 mg h/L) compared with those with no adverse effects (MPA AUCfree 1.1 ± 0.1 mg h/L). However, inconsistent with Kuypers et al. [29], the relationship was lost when total exposure was characterized (Table 1).

Furthermore, in a longer term, 5-year follow-up study using a categorical approach, Kuypers et al. [6] were able to estimate the exposure thresholds for developing hematological toxicities. In this study, an exposure-effect relationship was clearly evident in subjects with leukopenia (AUC < 30 mg h/L [5%] vs. AUC 30–60 mg h/L [7%] vs. AUC > 60 mg h/L [12.4%]), anemia < 12 g/L/day (AUC < 30 mg h/L [40.8%] vs. AUC 30–60 mg h/L [52.2%] vs. AUC > 60 mg h/L [64.3%]), or anemia < 10 g/L/day (AUC < 30 mg h/L [14.2%] vs. AUC 30–60 mg h/L [17%] vs. AUC > 60 mg h/L [25%]). These findings provided support for using an MPA AUC cut-off of 60 mg h/L for the detection of leukopenia or anemia, but further receiver operating characteristic analyses are needed to establish the specificity and sensitivity of this specific threshold. Finally, in a corticosteroid-free population, Kiang et al. [36] found significant correlations between total MPA exposure and neutropenia in three different periods within the first year of transplant (Table 1). While a strong correlation was observed, further analyses are still needed to identify the specific MPA AUC thresholds for developing neutropenia. As well, the relationship between MPA exposure and neutropenia still remains to be established in the corticosteroid-based population.

Similar to other discussed side effects, a large number of studies have not supported an MPA exposure-hematological toxicity relationship, irrespective of MPA formulation or patient ethnicity (Table 1). In a prospective, double-blinded, concentration-controlled study, the incidences of leukopenia within 6 months of a transplant were not statistically significant between patients with different levels of MPA exposure, although a trend was identified where subjects having elevated AUCs (96.7 ± 32.2 mg h/L) appeared almost twice more likely to develop neutropenia [5]. In a randomized prospective controlled study by van Agteren et al. [26], 16% of the subjects were found to have developed leukopenia between 3 and 12 months post-transplant; but, this was only observed in the tacrolimus, and not cyclosporine, co-treated patients. No difference in acyl MPA glucuronide exposure (measured at month 3) in patients with (1.36 mg h/L) or without (1.15 mg h/L) leukopenia was identified in this study. Similarly, Gaston et al. [30] did not report a difference in the incidence of leukopenia between concentration-controlled or fixed-dosing MPA regimens with either normal- or reduced-dose calcineurin inhibitor co-administration. In support of these findings, Sobiak et al. [37] found no consistent associations between MPA or MPA glucuronide exposures and levels of hemoglobin (some correlation with glucuronide observed), hematocrit, erythrocyte count, leukocytes, or platelets in their relatively lengthy (4.7 years) observational study. Furthermore, in a series of studies that have examined the effects of intensified vs. standard dosing (of either MPA formulation), early increases in MPA AUCs did not generally translate to increased incidences of hematological disorders over 3 months [20], 6 months [17, 21, 23], or 12 months [16, 22, 24] post-transplant. More

specifically, in individuals with an MPA AUC ≤ 60 mg h/L vs. an MPA AUC > 60 mg h/L, Gourishankar et al. [17] found no difference in the incidence of leukopenia (20 vs. 18.4%), neutropenia (5.0 vs. 5.3%), and thrombocytopenia (3.8 vs. 2.6%). Moreover, based on the study by Arns et al. [22], it was clearly evident that the majority of the hematological events (e.g., leukopenia, thrombocytopenia, anemia) occurred within the first 6 months post-transplant, an observation that is consistent with the other identified adverse effects of MPA (Table 1).

4 Conclusion and Future Directions

The overall collective data can be best described as inconclusive to support a relationship between MPA exposure and the manifestation of specific (i.e., GI, infection, or hematological) adverse effects. While promising exposure thresholds (i.e., > 40–60 mg h/L for total MPA) or exposure-toxicity correlations for MPA have been suggested by a few studies presented in this review, many were observational in nature and of relatively short duration. Furthermore, the limited and conflicting experimental evidence supporting free MPA exposure or MPA metabolites as potentially better markers of toxicity indicates that further validations are required. The number of papers with negative findings also outnumbered those that have reported associations (Table 1). With respect to clinical factors affecting MPA toxicity, concurrent calcineurin inhibitor administration (i.e., either tacrolimus or cyclosporine) does have significant effects on MPA exposure, but clear relationships with MPA-associated toxicity have not always been documented (Table 1). Tornatore et al. [27] suggested that female subjects were more likely to develop GI adverse events, but the majority of other studies have not conducted sex-based analyses. Moreover, although there does not appear to be significant differences in the MPA exposure-toxicity relationship based on ethnic makeup, the majority of the data were obtained from Caucasian-based populations (with the remaining from Asian subjects) with no single paper having conducted a properly controlled comparison (Table 1). Additional systematic analyses with other clinical markers (e.g., the type of transplant [live vs. cadaveric], age, induction therapy, or concurrent supportive medications) were also difficult because of the heterogeneous nature, limited number, and inconsistent reporting (i.e., with missing data) of the included papers (Table 1).

However, many confounding factors that could have attributed to false-negative findings were also evident in these studies. (1) In many cases, the identified toxicity may not be attributed to MPA alone, and other concurrent drugs (e.g., tacrolimus for diarrhea; type of induction therapy for infection or leukopenia) may have masked the contribution of MPA. Perhaps a "combined" therapeutic window as proposed by Kuypers et al. [29] might be able to mitigate part of this limitation with the co-administered maintenance immunosuppressant therapies. (2) The majority of the studies lacked sufficient power for detecting differences in toxicity events that were often characterized as secondary endpoints. Where power analyses have been conducted, they were mostly tailored to the primary end-point for MPA efficacy (i.e., rejection frequency). (3) The MPA-associated toxicities were often not consistently or clearly defined between the studies. As examples, different definitions based on individual center practices for diarrhea (with or without baseline consideration) or leukopenia/neutropenia (severity, cut-off) were evident. (4) Different analytical assays for MPA were used between studies, which could have resulted in different exposure estimations (Table 1). For example, several studies have utilized immunoassays that are known to over-estimate MPA concentrations as a result of cross-reactivity with the acyl MPA glucuronide. With the majority of centers now electing to use liquid-chromatography mass spectrometry for improved selectivity and sensitivity, it is unclear whether these historical data collected with different assays can still be relevant for current practice today. (5) With the exception of a few studies, the majority did not capture exposure data at the same time as the occurrence of MPA adverse events. Many studies were also designed to only increase early MPA exposure, which led to mostly negative associations with adverse outcomes that were captured over a longer period of time. The inconsistencies between the timing of MPA exposure estimation and the occurrence of toxicity could have severely minimized the sensitivity of the correlations. Finally, (6) the majority of the studies presented in Table 1 had a follow-up period within 12 months; therefore, very limited data on the longer term toxicity threshold, which may be different than the acute period (i.e., within the first year post-transplant), were available.

Collectively, we have summarized the literature that suggests promising MPA exposure-toxicity relationships in adult kidney transplant recipients. Although it is not yet possible to define toxicity threshold(s) for the purpose of therapeutic drug monitoring, the information obtained and the limitations identified in these studies have provided a good foundation for future investigations using properly powered, controlled, randomized, or blinded trials with the primary aim to investigate specific toxicities.

Compliance with Ethical Standards

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