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REVIEW

Do Asian renal transplant patients need another mycophenolate mofetil dose compared with Caucasian or African American patients?

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Summary

Mycophenolate mofetil (MMF) is used to prevent acute rejection following solid organ transplantation in transplant centers all over the world. Patients from different ethnic backgrounds are treated with this drug, for which therapeutic drug monitoring (TDM) has not become the standard of practice in most centers. Whether or not some ethnic groups require a different MMF dose has been a topic of debate in recent years. In this review, it is shown that Asian patients, compared with Caucasian patients, with a comparable MMF dose reach higher mycophenolic acid (MPA) exposure. Also clinical experience points toward more adverse events in case of treatment with 1 g MMF bid in Asian patients, and therefore, for this ethnic group, a lower maintenance dose seems justified. In contrast, African American patients reach similar drug concentrations as Caucasians patients receiving the same MMF dose, but due to immunological reasons, they require a higher MMF dose to reach comparable acute rejection incidences. When TDM is performed, clinicians can correct the dose and compensate for interethnic differences in drug exposure. Otherwise, it is important to choose the right dose. This optimal dose is 20–46% lower in Asian transplant recipients than in Caucasian or African American patients.

Introduction

Mycophenolate mofetil (MMF), a prodrug of the immunosuppressive agent mycophenolic acid (MPA), is widely used for the prophylaxis of rejection after solid organ transplantation. Following oral administration, MMF undergoes rapid and complete hydrolysis to form MPA. MPA is a potent, selective, uncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and thus exerts cytostatic effects on proliferating T lymphocytes and B lymphocytes by inhibiting the *de novo* pathway of guanosine nucleotide synthesis [1,2]. MPA is highly bound to serum albumin (approximately 97%), with the free fraction responsible for its action [3]. It has long been recognized that immunosuppressant pharmacokinetics exhibit ethnicity-specific differences in bioavailability and/or dose-adjusted systemic exposure, particularly cyclosporine A (CsA), tacrolimus (Tac), sirolimus, and everolimus [4]. Oral bioavailability of CsA and Tac in African Americans (AAs) is 20–50% lower than in Caucasians or non-African Americans [5]. Clearance of sirolimus and everolimus in AAs is 20–45% higher than in Caucasians, leading to higher dose requirements in AAs to maintain similar average concentrations of these immunosuppressants [6,7].

In clinical practice, the starting dose of MMF after renal transplantation is based on data from clinical trials carried out in America, Australia, Canada, and Europe [8–11]. The recommended total daily dose for Caucasian patients, on co-treatment with CsA, is 2 g/day (in two equally divided doses). Neylan *et al.* [8] reported that dose-dependent prevention of acute rejection in AAs was best afforded by an MMF dose of 3 g/day, whereas 2 g/day provided a superior benefit/risk ratio for non-AAs. The higher dose requirement in AA patients could not be explained by a difference in MPA exposure, as no significant differences in the pharmacokinetics of MPA were found between Caucasian and AA renal transplant recipients [8]. However, Tornatore *et al.* [12], suggested that an increase in MPA dose in AA males by approximately 35–40% was needed to maintain MPA concentration at similar levels to Caucasian males.

Personal communication with nephrologists in Asia has learned us that many Asian patients receive lower starting MMF doses (1.5 g/day) than patients in Europe or the U.S. As there is a significant correlation between MPA area under the plasma concentration-time curve (AUC) and clinical outcomes (acute rejection and adverse events) in renal transplantation, differences in MPA exposure based on ethnicity are of clinical relevance [13–17]. MPA exposure measured by $AUC_{0–12}$ gives the best prediction of the risk of rejection, and the target range is 30–60 mg·h/l for Caucasian patients [18]. There are no studies which specifically tried to validate this target range for other ethnicities. The range of 30–60 mg·h/l is also applied for Asian patients. The aim of this study was to review the literature regarding differences in MMF pharmacokinetics and provide the reader with an up-to-date comparison between Asian and Caucasian plus AA renal transplant patients.

Materials and methods

A National Library of Medicine (PubMed) search of the English language literature was performed using the following queries "pharmacokinetics" and "mycophenolate mofetil/mycophenolic acid" and "renal/kidney transplant patient", excluding "EC-MPS (enteric-coated mycophenolate sodium)". Additional search words were later used for specific topics (e.g., "Asian", "Caucasian", "African", "$AUC_{0–12}$", "ethnic difference", "race difference", "Adults", etc.). Manuscripts were included if they addressed the subject of this review. The papers included in this review had to provide accurate MPA-$AUC_{0–12}$/dose-normalized MPA-$AUC_{0–12}$, dose of MMF, and had to be clear about the time after transplantation. The percentage of the dominant ethnicity in the studied population had to be 80% or higher.

The review was structured to address the most important ethnic factors and differences involved in the pharmacokinetics of MMF/MPA between Asian and Caucasian/AA renal transplant patients: (i) comparison of dose-adjusted MPA systemic exposure in Asian and Caucasian/AA patients, and (ii) factors potentially contributing to ethnic differences in MPA pharmacokinetics.

Results

This literature review included 21 studies involving pharmacokinetic profiles of MPA in Asian and Caucasian/AA renal transplant patients. The data were arranged in four different groups, depending on the type of CNI with which the patient was co-treated (CsA or Tac) and depending on time after transplantation (<6 or >6 months post-transplant). A detailed overview of MPA exposure data from the papers included in this review can be found in Tables 1a [19–26], 1b [19,24,27–32], 2a [12,25,33–36], and 2b [19,29,30,37,38]. Overall, the dose-normalized MPA-$AUC_{0–12}$ was higher in Asian than in Caucasian/AA patients and similar for Caucasian and AA patients.

Comparison of MPA-$AUC_{0–12}$ in Asian and Caucasian/AA populations co-treated with CsA within the first 6 months post-transplant shows that the dose-normalized MPA-$AUC_{0–12}$ in Caucasians [19,21,23] is lower than in Asians [20,22,24] (Table 1a). The exception is the study by Liang [26], who found MPA-AUC values that were comparable with Caucasian patients. The interval from transplantation to blood sampling, a well-known factor that influences MPA clearance, cannot explain the results of the study by Liang that are different from the other studies in Asian patients. When co-treated with Tac, similar results were obtained (Table 1b). Also in combination with tac, the dose-normalized MPA-$AUC_{0–12}$ in Asians is higher than in Caucasian patients. The difference between Asian and Caucasian patients is even more pronounced than when combined with CsA (Table 1b). The interval since transplantation was highest in the study by Kuypers *et al.* [29] (6 weeks), and this may explain why in this study dose-normalized MPA exposure was higher than the other studies performed in Caucasians. The studies listed in Table 2a,b also support the observation that Asians patients have higher dose-corrected MPA exposure.

Table 1a,b clearly show that for all ethnicities the dose-normalized MPA-$AUC_{0–12}$ in patients co-treated with Tac is higher than if co-treated with CsA. The difference in MPA exposure between patients co-treated with CsA or Tac in the Asian population is more pronounced. A similar impact of the type of calcineurin inhibitors (CNIs) is found in pharmacokinetic studies performed in patients more than 6 months post-transplantation (Table 2a,b). Also, our data show that the dose-adjusted MPA exposures shown in Table 2a,b are higher than those in Table 1a,b, and

Table 1. (a) MPA-AUC_{0-12} in CsA co-treated renal transplant patients within 6 months post-transplant. (b) MPA-AUC_{0-12} in Tac co-treated renal transplant patients within 6 months post-transplant.

Ethnicity	No. of patients	Bodyweight/kg	Time post-transplant	MMF Dose/mg/day	MPA AUC_{0-12}/mg·h/l	Dose normalized MPA-AUC_{0-12}/h/l	Reference
(a)							
Caucasian	387		4 weeks	2325 ± 864	41.0 ± 14.8	0.035*	van Gelder *et al.* [19]
	22		4 weeks	2130 ± 320	36.4 ± 9.76	0.036 ± 0.010†	Shaw *et al.* [21]
	168	68 (38–151)	1 month	2000 (500–4400)	38.0	0.038†	van Hest *et al.* [23]
	32	70.2 ± 11.4	3 months	2000	42.9 (39.8–50)	0.043†	Kuypers *et al.* [25]
Asian	75	58.2 ± 9.7	2 weeks	2000	53.0 ± 15.1	0.053*	Zhou *et al.* [20]
	31	60.3 ± 9.3	7 days < *t* < 2 months	2000	52.16 ± 12.50	0.052*	Zicheng *et al.* [22]
	22	58.0 ± 10.0	Within 7 days	2000	48.2 ± 10.7	0.048*	Lu *et al.* [24]
	22	56 ± 10.3	12 days	2000	33.9 ± 8.9	0.034*	Liang *et al.* [26]
African American	13		4 weeks	2170 ± 390	42.1 ± 18.5	0.042 ± 0.019†	Shaw *et al.* [21]
	7		1 month	2000 (500–4400)	30	0.030†	van Hest *et al.* [23]
Total/Average‡							
Caucasian	609	79.5 ± 18.6	4.4 weeks	2273 ± 774	40.2 ± 12.1	0.036	
Asian	150	58.2 ± 9.7	3 weeks	2000	49.3 ± 14.7	0.049	
AA	20		4 weeks	2200 ± 630	37.9 ± 15.9	0.038	
(b)							
Caucasian	319		4 weeks	2034 ± 716	54.3 ± 22.8	0.053*	van Gelder *et al.* [19]
	67	77.7 ± 19.4	5 days	1990 ± 140	46.8	0.047*	Gourishankar *et al.* [28]
	33		6 weeks	1740 ± 510	59.9 (18.6–211.0)	0.066 ± 0.038†	Kuypers *et al.* [29]
	29	78.0 ± 18.0	5 days	2000	40.0 ± 12.1	0.040 *	Kiberd *et al.* [31]
Asian	40		4 weeks	1500	71.1 ± 25.0	0.095*	Kagaya *et al.* [27]
	7	58.0 ± 10.0	Within 7 days	2000	60.95 ± 11.68	0.061 *	Lu *et al.* [24]
	50	54.1 ± 10.1	4 weeks	1500	63.9 ± 28.9	0.085*	Miura *et al.* [30]
	57	55.8 ± 11.8	4 weeks	1572 ± 310	87.0 ± 40.0	0.087 ± 0.040†	Miura *et al.* [32]
African American	No data available						
Total/Average‡							
Caucasian	448	77.8 ± 18.9	3.5 weeks	2023 ± 649	54.6 ± 25.5	0.052	
Asian	154	55.2 ± 10.9	3.9 weeks	1568 ± 130	70.4 ± 25.4	0.087	
AA							

*Dose normalized AUC_{0-12} not given in the literature, estimated by AUC_{0-12}/MMF single dose (mg).
†Dose normalized ACU_{0-12} given in literature, normalized by MMF single dose (mg); AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; MPA, mycophenolic acid. Values are expressed as mean ± SD or median (range).
‡the data (mean ± SD) pooled by the method "eMath zone", (http://www.emathzone.com/tutorials/basic-statistics/combined-variance.html).

confirms that MPA exposure increases with time after transplantation.

Based on the data shown in Tables 1a,b and 2a,b, the ratios of dose-normalized MPA-AUC_{0-12} between Asians and Caucasians were 1.36, 1.67, 1.25, and 1.84, respectively. In order to reach the same target range for Caucasians, estimated reduction of the dose for Asian renal transplant patients is about 20–46%.

Discussion

In this literature review, we have analyzed whether the pharmacokinetics of MPA are different between Asian renal transplant recipients on the one hand and Caucasian and AA kidney transplant patients on the other. The influence of the type of CNI (CsA or Tac) and the time after transplantation (<6 or >6 months post-transplant) were also investigated. The main finding of this review is that Asians have higher dose-corrected MPA-AUC_{0-12} than Caucasians/AAs after similar time post-transplant. We confirm that the type of CNI has an impact on MPA pharmacokinetics and that MPA exposure increases with time after transplantation. Several studies have shown that different combinations of drugs in immunosuppressive regimens result in differences in MPA exposure [39–43]. This difference can be explained by reduced entero-hepatic circulation (EHC) of MPA-Glucuronide (MPAG) in case of CsA co-treatment due to inhibition of the multidrug resistance-associated protein (MRP)-2 [44]. The increase in MPA exposure over time has been indicated in a number of studies, also if a fixed MMF dose is used or even despite small MMF dose reductions are performed [45–48]. This

Table 2. (a) MPA-$AUC_{0–12}$ in CsA co-treated renal transplant patients more than 6 months post-transplant. (b) MPA-$AUC_{0–12}$ in Tac co-treated renal transplant patients more than 6 months post-transplant.

Ethnicity	No. of patients	Bodyweight/kg	Time post-transplant	MMF Dose/mg/day	MPA $AUC_{0–12}$/mg·h/l	Dose normalized MPA-$AUC_{0–12}$/h/l	Reference
(a)							
Caucasian	14	102.6 ± 16.8	7.7 ± 4.5 years	1964 ± 414	42.7 ± 18.4	0.060 ± 0.025†	Tornatore *et al.* [34]
	36	80.9 ± 18.3	4.1 ± 3.2 years	1330 ± 384	42.2 ± 17.5	0.070 ± 0.030†	Tornatore *et al.* [12]
	43	79.3 ± 11.62	3.3 ± 2.3 years	2023 ± 153	55.0 ± 18.7	0.055†	Pescovitz *et al.* [35]
	25	70.2 ± 11.4	1 year	2000	49.1 (45.1–56.3)	0.049†	Kuypers *et al.* [25]
	101		2 years	1931 ± 34	42.4 ± 15.6	0.044*	Etienne *et al.* [36]
Asian	53	66.8 (33.1–108.1)	3.5 (0.3–15.3) years	1274 ± 411	41.4 ± 14.2	0.065*	Yau *et al.* [33]
African	13	97.9 ± 26.4	5.2 ± 3.4 years	1960 ± 660	38.4 ± 19.1	0.053 ± 0.019†	Tornatore *et al.* [34]
American	17	93.4 ± 17.0	3.1 ± 1.8 years	1716 ± 512	38.2 ± 17.3	0.050 ± 0.020†	Tornatore *et al.* [12]
	39	81.9 ± 13.9	2.1 ± 1.7 years	2205 ± 393	54.3 ± 14.4	0.054†	Pescovitz *et al.* [35]
Total/Average‡							
Caucasian	219	80.6 ± 17.0	2.8 years	1860 ± 309	45.7 ± 16.6	0.052	
Asian	53	68.7 ± 18.8	3.5 years	1274 ± 411	41.4 ± 14.2	0.065	
AA	69	87.8 ± 18.6	2.93 years	2038 ± 518	47.3 ± 17.1	0.053	
(b)							
Caucasian	28	70.4 ± 15.9	2.5 ± 1.9 years	1321 ± 509	31.5 ± 11.5	0.053 ± 0.027†	Poulin *et al.* [37]
	33		1 year	1520 ± 510	58.8 (27.7–111.0)	0.077*	Kuypers *et al.* [29]
	20	68.4 ± 16.4	3.3 ± 1.7 years	1263 ± 510	59.8 ± 28.3	0.059 ± 0.028†	Greanya *et al.* [38]
	222		1 year	1245 ± 533	45.1 ± 17.9	0.072*	van Gelder *et al.* [19]
Asian	70	59.7 ± 13.3	1 year	1000 (500–1500)	58.1 ± 24.3	0.116*	Miura *et al.* [30]
African American	No data available						
Total/Average‡							
Caucasian	303	69.5 ± 15.9	1.29 years	1282 ± 531	46.8 ± 20.3	0.063	
Asian	70	59.7 ± 13.3	1 year	1000 ± 250	58.1 ± 24.3	0.116	
AA							

*Dose normalized $AUC_{0–12}$ not given in the literature, estimated by $AUC_{0–12}$/MMF single dose (mg).

†Dose normalized $ACU_{0–12}$ given in literature, normalized by MMF single dose (mg); AUC, area under the concentration-time curve; MMF, mycophenolate mofetil; MPA, mycophenolic acid. Values are expressed as mean ± SD or median (range).

‡The data (mean ± SD) pooled by the method "eMath zone", (http://www.emathzone.com/tutorials/basic-statistics/combined-variance.html).

phenomenon is assumed to be the result of reduced MPA clearance associated with improvement of renal function, changes in the exposure to concomitantly administered immunosuppressive agents, especially CsA and glucocorticoids, and other factors changing with time after transplantation [49].

Many factors potentially contribute to ethnic differences in MPA pharmacokinetics, including bodyweight, EHC of MPAG, pharmacogenetics, diet, and environment.

In the majority of transplant centers, a fixed dose of MMF is prescribed for adult renal transplant patients, and doses are reduced in case of side effects. This dosing strategy does not take into account that in some populations, bodyweight on average may be relatively low, leading to a disproportionately high MMF dose per kg bodyweight. In pediatric patients, MMF dosing based on body surface area (600 mg/m^2 twice daily, with concomitant CsA and glucocorticoid) is routinely applied [50]. A number of studies show that the adult bodyweight differs among ethnicities [33]. The bodyweight distribution in the studies reported in Tables 1a,b and 2a,b is summarized in Table 3 [51], which shows that the bodyweight of Asians is much lower than that of Caucasians/AAs (59.1 ± 13.0 kg vs. 78.4 ± 17.9 kg, 59.1 ± 13.0 kg vs. 87.8 ± 18.6 kg, $P < 0.0001$).

Although bodyweight may seem to explain the differences in MPA exposure, there are data that suggest bodyweight is not an important determinant for exposure and that the differences observed are due to variability in clearance (CL). Funaki *et al.* [52] reported that the oral MPA CL was 25 l/h for Japanese and 45 l/h for Caucasians in their study ($n = 140$). This Japanese patient population also had a higher $AUC_{0–12}$ than Caucasians. Yau *et al.* [33] reported that in 53 Asian patients 3 months after renal transplantation, in 86.7% of patients, MMF dose was <2 g/day, but nevertheless the mean MPA-$AUC_{0–12}$ (41.4 ± 14.2 mg·h/l) was within the recommended therapeutic range, and MPA-$AUC_{0–12}$ had a weak but significant

Table 3. Bodyweight distribution of the three population in the literature (Tables 1a,b and 2a,b).

Caucasian Ref No.	*n*	Bodyweight/kg	Asian Ref No.	*n*	Bodyweight/kg	African American Ref No.	*n*	Bodyweight/kg
23	168	81.3 ± 18.3‡	20	75	58.2 ± 9.7	34	13	97.9 ± 26.4†
25	32	70.2 ± 11.4	22	31	60.3 ± 9.3	12	17	93.4 ± 17.0†
28	67	77.7 ± 19.4	24	29	58.0 ± 10.0	35	39	81.9 ± 13.9
31	29	78.0 ± 18.0	26	22	56.0 ± 10.3			
34	14	102.6 ± 16.8	30	50	54.1 ± 10.1			
12	36	80.9 ± 18.3	32	57	55.8 ± 11.8			
35	43	79.3 ± 11.6	33	53	68.7 ± 18.8‡			
25	25	70.2 ± 11.4	30	70	59.7 ± 13.3			
37	28	70.4 ± 15.9						
38	20	68.4 ± 16.4						
Total/Average‡	462	78.4 ± 17.9***		387	59.1 ± 13.0***		69	87.8 ± 18.6***

***Significant difference between Asian and Caucasian, and Asian and African American patients ($p < 0.0001$).
†The data (mean ± SD) pooled by the method "eMath zone", (http://www.emathzone.com/tutorials/basic-statistics/combined-variance.html).
‡Estimated the mean and variance from the median, range, and the size of sample [51]; Ref No. 23 original value: 68 (38–151) kg; Ref No. 33 original value: 66.8 (33.1–108.1) kg.

correlation with bodyweight-adjusted MMF dose ($r^2 = 0.30$). A subset analysis of the Opticept trial ($n = 219$) evaluated the effect of baseline bodyweight in three noncontiguous weight categories on MPA exposure at steady state in renal transplant patients receiving Tac and MMF. They demonstrated that CL increased with increased weight, resulting in an inverse relationship between dose-corrected MPA-AUC and bodyweight [53]. Also Guillet *et al.* [54] found that bodyweight was a significant covariate of the inter- and the intra-individual variability of MPA exposure. In the studies of Le Guellec *et al.* and Staatz *et al.* [55,56], a trend toward increased MPA clearance with higher bodyweight was also found. These studies provide some evidence to support that bodyweight does influence MPA pharmacokinetics. Other large trials did not show a correlation between bodyweight and MPA pharmacokinetics [23,47,57].

Mycophenolate mofetil is rapidly absorbed and metabolized to the inactive 7-O-MPAG, which undergoes EHC, resulting in a smaller second MPA plasma peak 6–12 h after MMF intake [58–60]. The contribution of this EHC to the overall pharmacokinetics of MPA is about 40% [52], with a range of 10–60% [61]. Jiao *et al.* [62] reported that the amount of MPA recycled in the body was estimated to be 29.1% of the total amount absorbed in Chinese healthy volunteers. EHC is a complicated process and can be influenced by a range of factors such as co-medication, diet, genetic variability, and other patient characteristics. Only a few population pharmacokinetic models have included the EHC on the total exposure, and none of these studies has studied the impact of ethnicity on the contribution of EHC.

Within the area of pharmacogenetics, an increasing number of studies investigated the influence of "race" and "ethnic background" in clinical medicine, which has been referred to as "racial profiling". Several single-nucleotide polymorphisms (SNPs) have been identified in genes of enzymes involved in MPA pharmacokinetics. It was demonstrated that the SNPs in the MPA-metabolizing UGT isoenzymes, mainly UGT1A9, and as well as in the drug transporter MRP-2, explain part of the variability in MPA pharmacokinetics [44,63,64]. The interethnic differences in MPA pharmacokinetics can be caused by differences in the prevalence of these SNPs.

At least 16 UGT isoforms have been identified in humans [65]. UGT1A9 is the major isoform involved in MPA clearance. Lower CL was reported in *UGT1A9*1c* -440C>T/-331T>C and *UGT1A9*3* 98T>C carriers, concordant with the lower enzymatic activity associated with these SNPs, while higher CL was observed in *UGT1A9*1* -275T>A/-2152C>T carriers [66–70], SNPs that lead to a decrease in MPA-AUC_{0-12} of up to 50% [66,71,72]. The population frequency of these three variants among Caucasian, Asian, and African population is different. The frequency of *UGT1A9*1c* -440C>T/-331T>C and *UGT1A9*1* -275T>A/-2152C>T carriers in Caucasians is 42% and 15%, in Africans 8% and 28%, and in Asians 2% and absent. The frequency of *UGT1A9*3* carriers in Caucasian is from 0.63% to 3.6%, but no data for Asians and African are available [72,73]. Stingl *et al.* [74] in their meta-analysis demonstrated that heterozygous Caucasian carriers of the *UGT1A9*3* variant might benefit from receiving only about 70% of the average dose, and *UGT1A9*1* -275T>A/-2152C>T carriers (allelic variant frequency: African > Caucasian > Asian, Fig. 1) may need higher than average doses.

Variants in the *UGT2B7* gene are associated with a significantly higher AcMPAG/MPA ratio due to an increased

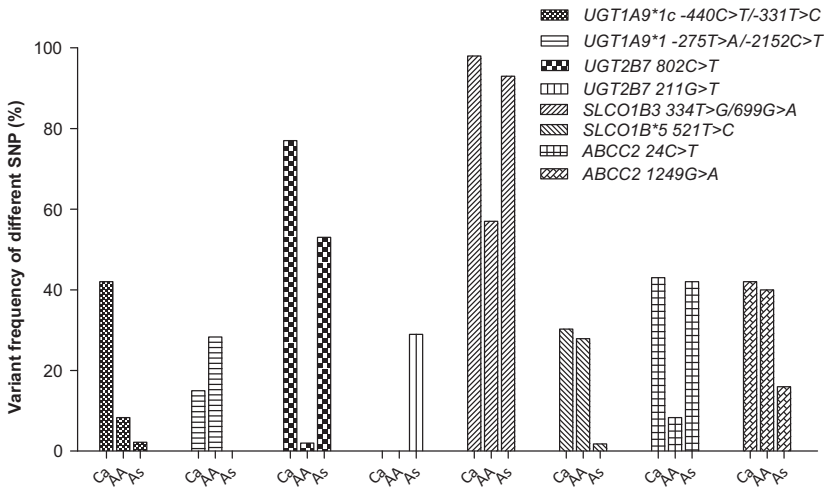

Figure 1 Variant frequency of mycophenolic acid PK related SNP among Caucasians (Ca), African American (AA), and Asians (As); data source is based on Hapmap.

production of AcMPAG. Although glucuronidation is generally considered a detoxification route of drug metabolism, the chemical reactivity of acyl glucuronides has been linked to MPA-related side effects [75]. There is no real evidence that *UGT2B7* SNPs have any independent influence on MPA pharmacokinetics [72]. The variant frequency of *UGT2B7* 802C>T is significantly higher in Caucasians and Asians than in AAs (77% and 53% vs. 2%) [72]. *UGT2B7* 211G>T was found in Asians in 29% [74]. The ethnic variation in the prevalence of *UGT2B7* SNPs may be responsible for differences in the incidence of adverse events related to MPA and therefore in dose reductions initiated in these patients.

Biliary excretion of MPAG involves several transporters, including the organic anion transporting polypeptides [76–78] (OATPs, encoded by *SLCO* genes) and MRP-2 [77,79] (encoded by *ABCC2*). Polymorphisms leading to altered OATPs and MRP-2 activity may therefore affect MPA pharmacokinetics [76,78,79]. The association of *SLCO* SNPs with MPA pharmacokinetics remains unclear. In the literature, there are conflicting data regarding the influence of gene polymorphisms in *SLCO1B3* 334T>G and 699G>A on MPA pharmacokinetics [76,80–83]. Different frequencies of these SNPs were found among the three populations studied. In Caucasians and Asians, the *SLCO1B*5* 521T>C variant is more prevalent (Caucasians and Asians about 30% vs. AAs 2%), whereas the *SLCO1B3* 334T>G and 699G>A variants are more prevalent in Caucasians and Asians than in Africans (98% and 93% vs. 57%, respectively).

A number of studies have been conducted to investigate the consequences of genetic polymorphisms in the *ABCC2* gene for the pharmacokinetics of MPA [67,69,71,76,79,81,84,85]. The most studied SNPs in this gene are the *ABCC2*−24C>T and 3972C>T SNPs, which are in linkage disequilibrium. Multiple studies reported no association between *ABCC2*−24C>T/3972C>T SNPs and MPA exposure, regardless of whether recipients were co-treated with CsA [67,71,84] or Tac [69,76,81]. Two studies did find an impact on MPA exposure [76,79]. The variant frequency of −24C>T SNP in Caucasians and Asians is significantly higher than that in AAs (43% and 42% vs. 8%) [72].

Obviously, diet is different between Caucasians and African American patients compared with Asian patients. However, there are no data that suggest dietary composition has an impact on MPA pharmacokinetics. In a study on 12 patients with rheumatoid arthritis, it was shown that MPA-AUC_{0-24} was statistically equivalent in fed and fasted state [85].

Based on our review, we conclude that Asian patients do have different pharmacokinetics for MPA, and the lower MMF maintenance dose which is applied in Asian compared with Caucasian patients is supported by our data. A randomized-controlled trial conducted in Asian renal transplant patients suggested the need for MMF dose reduction in this specific population to minimize the incidence of leucopenia [86]. Studies in Chinese renal transplant patients have suggested that an MMF dose of 1.5 g/day results in comparable efficacy as a standard 2 g/day dose but with less adverse events [87,88]. Lower required doses of MMF have also been reported for Thai (0.5–2 g/day) [89,90], Korean (1–1.5 g/day) [91], Japanese (0.25–2 g/day) [92–95], and Chinese (0.5–2 g/day) [33] renal transplant patients. There do not seem to be major difference between Chinese, Japanese, Thai, or other Asian populations. Overall,

the optimal MMF dose should be lower in all Asians patients.

For EC-MPS, there were only few studies in Asian patients available, but we do assume that the influence of race on MMF is also present in EC-MPS-treated patients. Two small studies do support the assumption that also in EC-MPS-treated patients, the MPA-AUC is higher in Asians than that in Caucasians. In one study performed in Chinese renal transplant recipients, conventional EC-MPS dosing resulted in a high MPA-$AUC_{0–12}$ (mean 61.2 mg·h/l), whereas in another study from China, low-dose EC-MPS treatment (540 mg bid) still resulted in MPA-$AUC_{0–24}$ of 44.7 mg·h/l [96,97].

Dose adjustment for both two formulations in Asians is of particular importance, as Asian populations are the fastest growing transplant populations worldwide, and obviously data obtained from European or US trials have to be validated in Asian populations. More controlled clinical trials are urgently needed to find the optimal dose for Asian patients.

Conclusions

This review summaries current knowledge on the MPA pharmacokinetics based on ethnic differences. It appears that with the same dosage, MPA systemic exposure is higher in Asian renal transplant patients than in Caucasians and American Africans. Causes for this ethnic difference may relate to lower bodyweight and differences in EHC and pharmacogenetics. Asian patients have a significantly lower bodyweight than Western patients. Pharmacogenetic variability among the three ethnicities may explain differences in either clearance (UGT1A9) or EHC (ABCC2). Current data regarding the contribution of genetics to the response of an individual to MPA is limited and conflicting, but this is one of the most promising factors to explain the differences between interethnic populations. Further research among the three populations is needed to investigate the ethnic factors that affect MPA pharmacokinetics.

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