Comparative efficacy and safety of mizoribine with mycophenolate mofetil for Asian renal transplantation—A meta-analysis

Shuai Xing [a,*,1], Jun Yang [b,2], Xue Zhang [a,1], Ping Zhou [a,**]

[a] Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Key Laboratory of Ministry of Health, Key Laboratory of Ministry of Education, Wuhan, China
[b] Department of Gerontology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ARTICLE INFO

ABSTRACT

Objectives: Mizoribine (MZR) with its high safety and low cost has been widely used in Asia. It has been questioned whether high or low dose of MZR could obtain the efficacy and safety similar to mycophenolate mofetil (MMF) following renal transplantation. This meta-analysis was done to compare the efficacy and safety of high- or low-dose MZR with MMF for immunosuppressive therapy in renal transplantation.

Design and methods: Available data comparing MZR with MMF in renal transplant recipients were searched. Subgroup analysis was conducted according to the administration dosage of MZR. Trials were pooled using Meta-analysis software and confidence intervals were set at 95%.

Results: Altogether 1149 Asian patients from 7 RCTs and 9 cohort studies were included. The efficacy of different MZR doses put on par with MMF, but the safety was better than MMF. Specifically, recipients taking MZR favor significantly fewer episodes of leucocytopenia [RR 0.40 (0.26, 0.60)], gastrointestinal disorder [RR 0.54 (0.40, 0.73)], CMV infection [RR 0.47 (0.34, 0.64)] and more favorable outcome of hepatic dysfunction, although the difference failed to reach a statistical significance [RR 0.67 (0.44, 1.00)]. Unfortunately, hyperuricemia was significantly obvious in MZR group [RR 1.96 (1.47, 2.61)].

Conclusions: MZR is an effective and safe immunosuppressive agent and high-dose MZR can be recommended as an alternative to MMF following adult renal transplantation in Asia, but hyperuricemia and liver damage should be closely monitored during the medication period.

© 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc.

Introduction

Recent improvement in immunosuppressive therapy has been based on a concept that not only promotes patient survival and graft outcome, but also improves their living quality. The ideal immunosuppressive agent should be one that can achieve life-long tolerance within short-term use, and without serious side effects. The discovery of calcineurin inhibitors (CNIs), including cyclosporine (CsA) or tacrolimus (FK506), is recognized as a milestone for renal transplantation, but both of them have some toxic effects, especially nephrotoxicity [1]. To reduce the side effects of CNIs, various purine-synthesis inhibitors have been recommended. Azathioprine (AZA), an inhibitor of salvage pathway of purine synthesis, has been used in clinical renal transplantation for 40 years. Two most important side-effects [2], dose-related bone marrow toxicity and liver toxicity, make AZA being challenged by the newer generation of more specific inhibitors of de novo purine synthesis, such as mycophenolate mofetil (MMF) and mizoribine (MZR). In particular, although no obvious nephrotoxicity, hepatotoxicity or neurotoxicity is observed in MMF-treated patients, the major side-effects of MMF including gastrointestinal disorder, diarrhea, leucopenia and thrombocytopenia [3], and what's more, unmanageable viral infections and exorbitant price still confound clinicians. Fortunately, MZR, with an equal immunosuppressive effect to AZA, less toxicity and potent anti-virus effect, was approved for renal transplantation in Japan in 1984 [4]. However, MZR did not spread worldwide because some paper reported that MZR had fewer side-effects but was less potent in immunosuppression. Few introductions about MZR in Europe and the USA made it less popular since MMF became a first choice as an antimetabolite combined with CNIs and steroids for immunosuppression in renal transplantation [5].

The recent meta-analysis demonstrates that MZR is significantly superior to AZA in renal transplant recipients [6]. When compared MMF with AZA, MMF used with CNIs indeed confers a clinical benefit over AZA [7]. So, a logical question is: what was the efficacy and safety when we use MZR compared with MMF? A number of high-quality researches, including randomized controlled trials (RCTs) or cohort studies, have assessed the efficacy and safety of MMF versus MZR as maintenance immunosuppression regimens after renal transplantation in Asia, but previous results have not been consistent. Whether MZR could substitute MMF as the cornerstone regimen in maintenance immunosuppression after renal transplantation in clinical setting remains uncertain. Due to the small sample size, most individual trials rarely provide enough statistical power to show a difference between MMF and MZR therapeutic effect.

Based on the controversial conclusions among various trials, we conduct a meta-analysis including all the available clinical trials to compare the efficacy and safety of MZR with MMF, in order to provide more reliable evidence that may help guide transplant surgeons.

Materials and methods

Literature search strategy

To identify the relevant literature, searches of Medline (PubMed and Ovid), Cochrane Library, Embase, ISI web of science and two Chinese database (China National Knowledge Infrastructure and WanFang database) were conducted from January 2000 to May 2013. Search terms were constructed by using Boolean logic of the following keywords: (renal transplant or kidney transplant) and (mizoribine or bredinin or MZR) and (mycophenolate mofetil or MMF or MPA). Potentially relevant studies obtained via electronic search were extracted. Their abstracts and full texts were considered for further evaluation, and their references were manually searched for further complement. We excluded reports using Boolean operator "not": meta-analysis or review or animal studies. To maximize data requisition, we contacted some of authors whose article contained insufficient information. In undertaking this study, we followed recommendations made by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.

Inclusion criteria

Articles published in any language were considered by two independent reviewers if they fulfilled the following criteria: (1) they comparatively assessed at least one risk event associated MZR versus MMF; (2) studies were designed as RCT or cohort- or case–control researches; (3) they were done in adult renal transplant recipients, from both deceased and living donors, except for those receiving multi-organ transplantation; (4) MZR versus MMF as maintenance immunosuppression regimen after renal transplantation, supplemented by other one or two types of immunosuppression drugs; (5) studies aimed to compare the efficacy and safety of MMF with MZR, without setting any dose limitation to MZR. If results from different follow-up populations were published by the same author, they were all included; for studies that used the same study population as another or others, we selected one of the highest qualities.

Data extraction and quality assessment

Two investigators independently extracted the data, utilizing a pre-designed data extraction form which met the inclusion criteria above. Disagreements between investigators with regard to data extraction were resolved by discussion and reached a consensus with all authors. Studies were classified according to their design. The following data, though some studies did not include all of them, were extracted from identified trials: (1) study characteristics relating to demographics, therapeutic regimen, dosage, duration of follow-up, etc; (2) efficacy

profiles, including acute rejection (AR), patient survival, graft survival and serum creatinine level (sCr); and (3) safety profiles, consisting of leukopenia, liver damage, gastrointestinal disorder, hyperuricemia, and virus infection. Further, high-dose (≥ 3 mg/kg/d) or low-dose (<3 mg/kg/d) MZR was classified into subgroups to determine the different efficacy and safety comparing with MMF. We had identified that there is no significant difference between the two treatment groups among all included studies in terms of recipient sex, donor sex, donor source, donor age, human leukocyte antigen-locus A, locus B, locus DR and blood group ABO-compatibility before our meta-analysis starts.

Quality assessment was undertaken independently by at least two authors. Discrepancies were resolved by discussion with a third investigator, or consensus of the whole team when necessary. The quality of RCT studies was assessed using the Jadad score system [8] while the case–control or cohort studies were assessed by means of Newcastle–Ottawa Quality Assessment Scale (NOS) [9].

Statistical analysis

Freeware program Review Manager (version 5.0) was used for data manipulation and statistical analysis. Measures of interest were relative risk (RR) and associated 95% CIs. Continuous outcomes were presented as a standardized mean difference (SMD) because two studies reported the level of serum UA using μg/dL and other studies used mmol/L. All statistical tests were two-sided. In our analytical framework, fixed-effect model or random-effect model was used depending on the absence or presence of significant heterogeneity. The heterogeneity among trials evaluated by the χ^2-based Q testing (Statistical significance cut-off for the test of heterogeneity was set at 0.10) and I^2 statistics ($I^2 > 50\%$). The random-effect model adjusted for variability of results among trials provided a more conservative estimate of an effect using wider CI.

Publication bias was examined by a funnel plot of RR against RR. If there was evidence of publication bias, the funnel plot would be asymmetric. Further, we also conducted a sensitivity analysis, by excluding any single study each time. Subgroup analysis was conducted if there was significant heterogeneity.

Results

Search results and characteristics

The literature searches yielded 148 studies. Of these, we excluded 132 articles and the remaining 16 articles fulfilled the criteria for this systematic review. The detailed process of study selection and reasons for exclusion are presented in Fig. 1. Seven of 16 articles were RCTs, and nine were cohort studies. All case studies were published in fulltext, and nine of them were published in Chinese, seven in English. These studies of our review were involved in the following 10 provinces municipalities in China and several other countries in Asia: Central China (Hubei, Henan), South China (Jiangxi, Guangdong), East China (Shanghai, Zhejiang, Jiangsu), North China (Beijing, Jilin), West China (Shanxi), Japan and Korea. A total of 1149 Asian patients treated with MZR (N.550) or MMF (N.599) were involved in this review. A great majority of these cases were collected from hospitals. The main characteristics and the detail of the quality assessment of these studies were summarized in Table 1. Additionally, as the results from two separate trials (both of which met the inclusion criteria) were reported by the same author Yoshimura N, both of them were included and were labeled with Yoshimura N 2012, Yoshimura N 2013.

Quality assessment of RCTs analyzed demonstrated that only 2 of 7 studies had a Jadad score equal to 3 (28.8%), and with mean value 2.14, especially for the principle of blinding and allocation concealment (0% and 28.6%, respectively). The quality of included RCTs was slightly low. With regard to cohort studies, fortunately, the majority of the studies
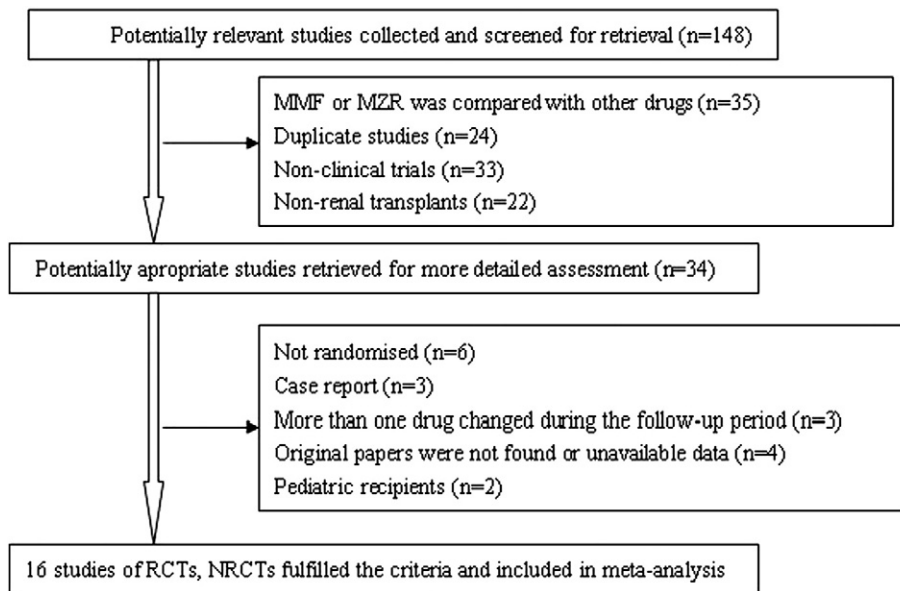
Fig. 1. Literature flow chart.

were of good quality with a total NOS score more than 6 (Mean:7.22). A major weakness in these studies was the shortness of the follow-up period, averaging 16 months (Table 1).

Efficacy profiles

Acute rejection

Incidences of AR were reported in 15 studies. Pooled results failed to show statistically significant differences between MMF and MZR group and no heterogeneity was observed. On the whole, MMF was associated with a lower incidence of AR over MZR despite no statistical difference. Such superiority reduced when a patient received higher dosage of MZR (Fig. 2 and Table 2).

Patient survival and graft survival

Data concerning patient or graft survival was available in 9 trials including 518 patients. Patients receiving low-dose MZR seemed to have lower patient or graft survival rates compared to those with MMF treatment, although such difference did not reach statistical

significance ($P = 0.80$ or $P = 0.61$, respectively). However, it should be noted that such superiority was reversal when patients received high-dose MZR, without significant heterogeneity detected. Similarly, no statistical significance was detected in terms of high-dose MZR versus MMF (Fig. 2 and Table 2).

Graft function

Similar results were yielded with respect to serum creatinine (sCr). No statistical significance was shown between groups no matter what doses that MZR consumes. The heterogeneity was high ($I^2 = 83\%$), but completely disappeared only when the study by Chen et al. was excluded from analysis. In particular, distinguishing from other included studies, Chen's study showed a significant increase of sCr in patients who were receiving MZR at the months 6 and 12 after renal transplantation. In our meta-analysis, the final available data of sCr was collected from the measured value at endpoints of monitoring therapy. Due to the difference of follow-up period (6, or 12, or 24 months), different values of sCr incorporated into this meta-analysis may partially explain the heterogeneity among studies. Overall, no noticeable MZR-related sCr

Table 1
Characteristic and quality assessment of included trials.

First author, year (reference)	Location	Study design	NO.(MZR/MMF)	Male(MZR/MMF)	Dosages		CMS	Donor type	Follow-up(M)	Jadad	NOS score
					MZR(mg/d)	MMF(g/d)					
Zhan SL [14]	North China	RCTs	30 (15/15)	21 (11/10)	180	1.5	CsA + Pred	NS	3	2	–
Zhang LY [15]	West China	RCTs	112 (52/60)	70 (32/38)	200	1.5	CsA + Pred	NS	18	3	–
Liu B [16]	Central China	RCTs	28 (14/14)	19 (NS)	72	1.5–2	CsA + Pred	LD	6	2	–
Han S [17]	East China	RCTs	70 (35/35)	46 (23/23)	200	1.5–2	CsA + Pred	DD	12	1	–
Ming AM [18]	South China	RCTs	40 (20/20)	NS	100	1.5	CsA/FK + Pred	DD	6	2	–
Takahara S [19]	Japan	RCTs	35 (16/19)	24 (9/15)	720	2	FK + St	LD	12	3	–
Ju MK [20]	Korea	RCTs	219 (110/109)	70/64	150–200 200 ~ 300	1–2 2	FK + Pred	LD or DD	6.5	2	–
Li XC [21]	South China	Cohort	62 (28/34)	NS	100	1.5	CsA/FK + Pred	LD	6	–	7
Chen JS [22]	East China	Cohort	69 (38/31)	46 (26/20)	100–150	1.5	CsA/FK + Pred	NS	12	–	8
Jang LN [23]	North China	Cohort	91 (32/59)	NS	100–200	1–1.5	FK + Pred	DD	6	–	9
Han L [24]	Central China	Cohort	112 (56/56)	NS	100	1–2	CsA + Pred	NS	12	–	6
Ohashi Y [25]	Japan	Cohort	37 (18/19)	28 (14/14)	300	1	FK	LD	39	–	7
Ding X [26]	East China	Cohort	72 (36/36)	25 (13/12)	100	1–1.5	CsA + Pred	LD or DD	>24	–	8
Yoshimura N [27]	Japan	Cohort	78 (40/38)	43 (23/20)	360	1.5	CsA + Bas + St	LD	24	–	7
Yoshimura N [28]	Japan	Cohort	24 (12/12)	13 (7/5)	360	1	CsA/FK + Pred	LD	12	–	6
Nakamura N [29]	Japan	Cohort	43 (22/21) 27 (6/21)	29 (15/14) 20 (6/14)	60–180 360	1–2	CsA/FK	LD or DD	>3	–	7

MZR: Mizoribine; MMF: Mycophenolate mofetil; CsA: Cyclosporin A: Bas: Basiliximab; FK: Tacrolimus; Pred: Prednisone; NS: Not specified; DD: Deceased donor; LD: Living donor; AC: Allocation concealment; ITT: Intention-to-treat; CMS: Combined medication scheme.
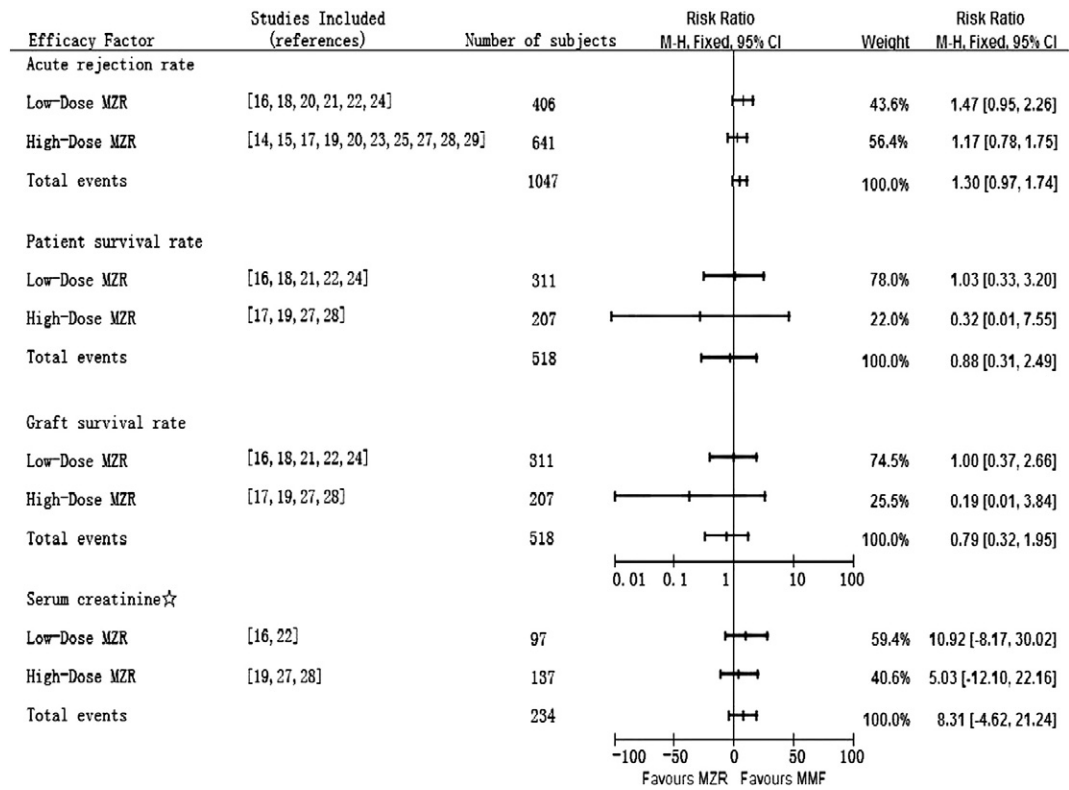
Fig. 2. Evaluation of pooled efficacy profiles of MZR comparing with MMF. The pooled relative risk (*RR*) with its 95% *CI* is depicted as a line segment. The position of the midpoint represents the *RR* value. *RR* more than 1 favors MMF, suggesting that less acute rejection episodes occurred in MMF group; *RR* less than 1 favors MZR, suggesting that less patient and graft survival episodes occurred in MZR group, but all without statistical difference. For the same reason, less elevated serum creatinine episodes occurred in MMF group comparing with MZR group but without statistical difference. M–H Fixed: Mantel–Haenszel Fixed-effects model; *CI*: Confidence Interval. ☆: The random-effect model was used for continuous variable due to heterogeneity evaluation of I^2 value 50%.

elevation was observed and no statistical significance was detected comparing with MMF [*RR* 8.31, 95% *CI* (−4.62, 21.24), *P* 0.21]. (Fig. 2 and Table 2).

Safety profiles

The safety profile was assessed by monitoring the occurrence of adverse events, including leukopenia, hepatic dysfunction, gastrointestinal disorder, virus infection and hyperuricemia. On the whole, except for hyperuricemia, MZR group had a significant lower incidence of adverse events compared to that of MMF without heterogeneity detected. The maintenance dose of MZR seemed no discernible

impact on the heterogeneity. In the analysis of specific variables, it was noted that patients receiving MZR had statistically significant fewer episodes of leukopenia and gastrointestinal disorder. Also, MZR seemed to offer more favorable outcome in terms of hepatic dysfunction. Although the liver damage was aggravated with increasing dose of MZR (Fig. 3 and Table 2), the difference never reached a statistical significance.

As for virus infection, the incidence of cytomegalovirus (CMV), Herpes zoster (HZV) and Polyomavirus BK (BKV) infection was reported in 11, 3 and 2 studies, respectively. MMF was associated with a higher incidence of CMV infection over MZR under homogenous conditions. However, no difference was detected in terms of HZV or BKV infection (*P* 0.75 or

Table 2
Meta-analysis of efficacy and safety outcomes.

Outcome	Studies reporting outcome (n)		MZR dose (*RR*, 95% *CI*)		Combined outcome			
	Studies	Patients	Low-dose	High-dose	RR	95% *CI*	P	I^2 (%)
Efficacy profiles								
Acute rejection	15	1047 (505/542)	1.47 (0.95–2.26)	1.17 (0.78–1.75)	1.30	0.97–1.74	0.08	0
Patient survival	9	518 (259/259)	1.03 (0.33–3.20)	0.32 (0.01–7.55)	0.88	0.31–2.49	0.80	0
Graft survival	9	518 (259/259)	1.00 (0.37–2,66)	0.19 (0.01–3.84)	0.79	0.32–1.95	0.61	0
Elevated sCr[a]	5	234 (120/114)	10.92 (−8.17–30.02)	5.03 (−12.10–22.16)	8.31	−4.62–21.24	0.21	83
Safety profiles								
Leukopenia	11	641 (303/338)	0.42 (0,25–0.72)	0.37 (0.20–0.71)	0.40	0.26–0.60	<0.0001	0
Liver damage	7	469 (239/230)	0.50 (0.26–0.94) [*]	0.86 (0.51–1.46)	0.67	0.44–1.00	0.05	0
GI disorder	11	840 (402/438)	0.39 (0.19–0.82)	0.59 (0.43–0.82)	0.55	0.41–0.74	<0.00001	50
CMV infection	11	542 (264/278)	0.30 (0.12–0.75)	0.51 (0.37–0.71)	0.47	0.34–0.64	<0.00001	15
HZV	3	81 (33/48)	NA	NA	0.80	0.19–3.26	0.75	0
BKV	2	72 (34/38)	NA	NA	0.67	0.09–4.87	0.69	0
Hyperuricemia	9	514 (252/262)	2.21 (1.45–3.36)	1.74 (1.17–2.58)	1.96	1.47–2.61	<0.00001	0

NA: Not applicable; GI: Gastrointestinal; sCr: Serum creatinine; CMV: Cytomegalovirus; HZV: Herpes zoster virus; BKV: Polyomavirus BK; *RR*: Relative risk; *CI*: Confidence interval.

[a] Random effects analysis.

[*] *P* = 0.03.

P 0.69, respectively). The small number of studies included made it difficult to draw firm conclusions with regard to either of these viral infections.

Nevertheless, the incidence of hyperuricemia was reported in 9 studies (514 patients). A significant increase in the risk of hyperuricemia was observed with MZR [RR 1.96, 95% CI (1.47, 2.61), P < 0.00001]. No heterogeneity was found and the dose-dependent effect was found between MZR and hyperuricemia risk (Fig. 3 and Table 2).

Publication bias evaluation and sensitivity analysis

There was no indication of a publication bias in the report of results on the efficacy and safety of MZR versus MMF, from visualization of the funnel plot (Fig. 4) which illustrated scarcely any of the included studies lay outside the 95% confidence interval boundaries. Via omitting one study at a time, the summary estimates for the outcome did not change significant difference, demonstrating that our results were statistically reliable.

Discussion

The immunosuppressive effects of MMF and MZR result from antipurine metabolite action. Both of them are uncompetitive and reversible inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH), potently interrupt DNA synthesis in the S phase of cell cycle, and thus suppress lymphocyte proliferation. What is the difference between them? The answer in this case may be concluded that MMF also prevents the glycosylation of adhesion molecules that are involved in the attachment and infiltration of lymphocytes; while the active form of MZR (MZR-5′-phosphate) affects both IMPDH and GMP synthetase, the latter is not inhibited by MMF [3]. According to conventional wisdom, MMF is used more widely because of its stronger effects than MZR for immunosuppression. However, MZR has been reported to display antiviral as well as immunosuppressive effects. In order to combine the effects of

anti-rejection with anti-virus, a high-dose MZR regimen revealed good results [10]. Because of the predominant renal metabolism, the dosage of MZR should be adapted to the glomerular filtration rate and MZR plasma trough level to avoid overimmunosuppression and adverse effects. As MZR passes a cell membrane according to the gradient of its concentration, currently, most of the RCTs from Japan are conducted to prove the efficacy and safety of high-dose MZR, distinguishing from the low-dose MZR use previously [10,11].

In this study, we examined whether high-dose MZR ($\geqq 3$ mg/kg/d) was as effective and safe as MMF for patients at a stable phase after renal transplantation. Based on their recommended dose respectively, the immunosuppressive action of MZR is almost identical with MMF. However, the recommended dose of MMF is 50 mg/kg/d and there is the enormous variety on that of MZR, which is only 1–2 mg/kg/d [3]. To compensate for the relatively less potent immunosuppressive effect of MZR, high-dose MZR was recommended. Our meta-analysis shows that high-dose (3–6 mg/kg/d) MZR as maintenance immunosuppression regimen supplemented by other one or two types of immunosuppressive agents could achieve satisfactory immunosuppression with a lower rate of adverse events compared with MMF. However, given the varying immunologic conditions of individual patients, individualized protocol of MZR use should be established. More clinical RCTs are still needed to confirm the difference of efficacy between MMF and MZR, due to the lack of statistical significance of present data. Meanwhile, our analysis also confirmed that the safety of MMF is weaker than MZR, and the weakness still exists comparing with the high-dose MZR. From other perspective, high-dose MZR regimen may be as effective as MMF, but safety is stronger than MMF, but for hyperuricemia, which is the most common side effect in MZR-treated patients, can be easily controlled by allopurinol administration in most cases at present.

Viral infections are major problems of renal transplant recipients who are at an early stage after transplantation. It has been reported that more than 50% of seropositive and about 10% of seronegative transplant patients may develop a symptomatic CMV disease [12]. Administration of MMF is well known to be associated with CMV infection and
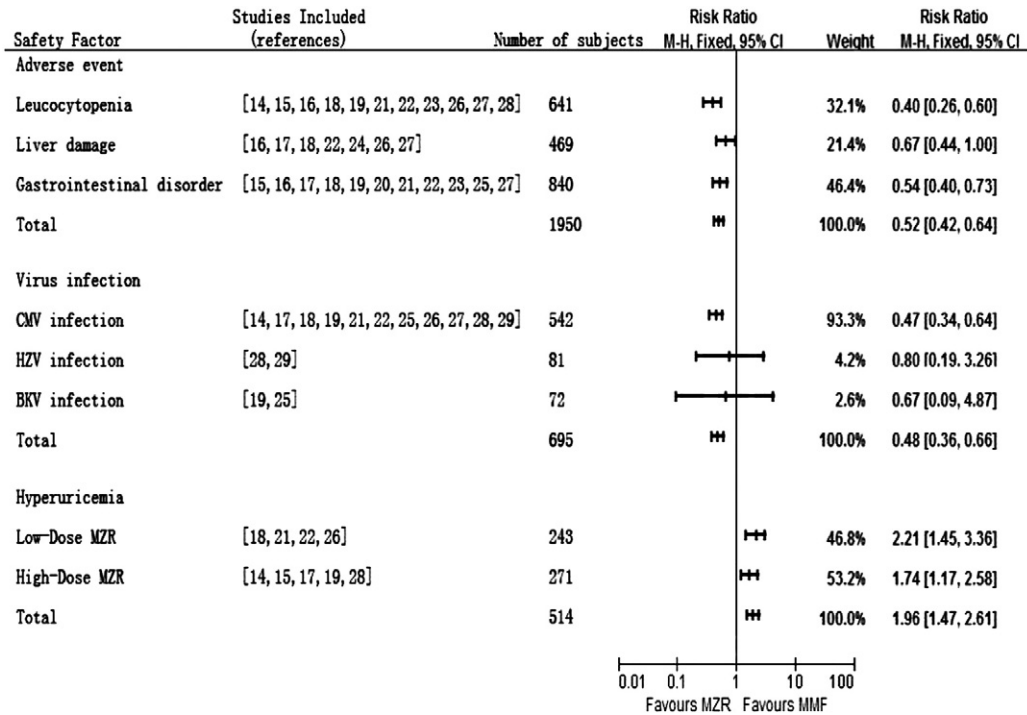
Safety Factor	Studies Included (references)	Number of subjects	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Adverse event					
Leucocytopenia	[14, 15, 16, 18, 19, 21, 22, 23, 26, 27, 28]	641		32.1%	0.40 [0.26, 0.60]
Liver damage	[16, 17, 18, 22, 24, 26, 27]	469		21.4%	0.67 [0.44, 1.00]
Gastrointestinal disorder	[15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 27]	840		46.4%	0.54 [0.40, 0.73]
Total		1950		100.0%	0.52 [0.42, 0.64]
Virus infection					
CMV infection	[14, 17, 18, 19, 21, 22, 25, 26, 27, 28, 29]	542		93.3%	0.47 [0.34, 0.64]
HZV infection	[28, 29]	81		4.2%	0.80 [0.19, 3.26]
BKV infection	[19, 25]	72		2.6%	0.67 [0.09, 4.87]
Total		695		100.0%	0.48 [0.36, 0.66]
Hyperuricemia					
Low-Dose MZR	[18, 21, 22, 26]	243		46.8%	2.21 [1.45, 3.36]
High-Dose MZR	[14, 15, 17, 19, 28]	271		53.2%	1.74 [1.17, 2.58]
Total		514		100.0%	1.96 [1.47, 2.61]

0.01 0.1 1 10 100
Favours MZR Favours MMF

Fig. 3. Evaluation of pooled safety profiles of MZR comparing with MMF. The pooled relative risk (RR) with its 95% CI is depicted as a line segment. The position of the midpoint represents the RR value. Forest plot shows the relative risk of the adverse event profile. Pooled estimates of leucocytopenia, liver damage, gastrointestinal disorder and virus infections compare MZR with MMF. RR value less than 1 favors MZR, suggesting that less episodes above occurred in MZR group, and vice versa, hyperuricemia more often occurred in MZR group and with statistical difference. RR: Relative Risk. M–H Fixed: Mantel–Haenszel Fixed-effects model; CI: Confidence Interval.
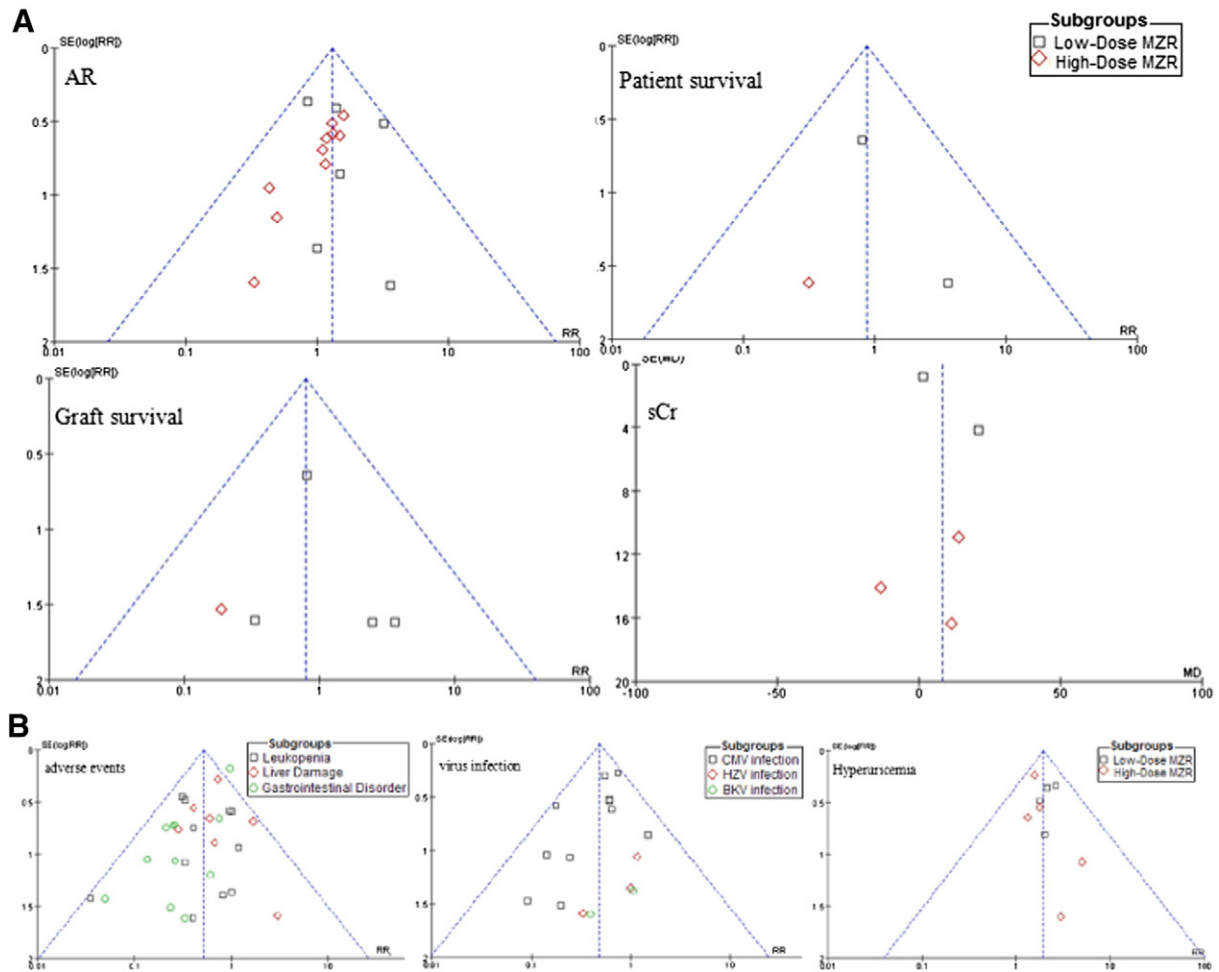
Fig. 4. Funnel plot of pooled efficacy and safety of MZR comparing with MMF. Vertical line shows overall relative risk, outer lines show 95% confidence interval. (A) efficacy profiles. (B) safety profiles.

BK nephropathy. Fortunately, MZR, with its similar chemical structure to ribavirin, a well-known broad-spectrum antiviral agent [13], shows anti-CMV activity in an apparently synergistic manner. Our meta-analysis reached the similar conclusion. Therefore, it is another reason for a positive recommendation for MZR use.

Medical cost is another consideration when we want to select an ideal immunosuppressive agent. Especially under the condition of comparable efficacy, medical expense may be an important consideration factor. As for the cost-effectiveness of MZR in Japan (Bredinin®), it would cost only 66.7% of MMF (CellCept®), comparing MMF 2 g/d with MZR 5 mg/kg/d for a patient weighting 50 kg. Similarly, in the case of China, MZR costs 55.9% of MMF, showing the similar anti-rejection effects [4].

Our meta-analysis has several potential limitations. (i) few of available data reported the HZV or BKV infection episodes, which limits our further subgroup analysis; (ii) the study quality of the included RCTs is relatively low, which might limit the ability to reach convincing conclusions; (iii) all the included trials were conducted among Asian populations, and no available data derived from Caucasians or black patient were collected, which limits the validity of this meta-analysis to Asian populations; (iv) some specific patient populations, such as living versus deceased donors, first graft versus multiple graft, or low- versus high-risk recipients, were not assessed due to the lack of enough available data. As such, our results should be interpreted with caution.

All in all, our meta-analysis provides evidence for the efficacy and safety of MZR use in Asian renal transplant patients. A high-dose MZR is expected to be as effective as MMF, as well as fewer adverse events,

but meanwhile, serum UA and liver damage should be monitored strictly. Given the lower cost and well-tolerated traits of MZR versus MMF in Asia, we recommend that more large-sample clinical trials with stricter design and longer follow-ups should be conducted to evaluate long-term efficacy and safety of MZR, especially in Europe and the United States, in order to make a possible improvement in overall renal transplantation around the world.

Conflicts of interest

The authors have no conflict of interest to disclose.

Acknowledgments

References

[1] Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. Am J Nephrol 2013;37:602–12.
[2] Jacob S, Rajabally YA. Immunomodulation in inflammatory neuropathies: rationale and safety. Curr Drug Saf 2013;8:225–35.
[3] Tsuzuki K. Role of mizoribine in renal transplantation. Pediatr Int 2002;44:224–31.
[4] Sugitani A, Kitada H, Ota M, Yoshida J, Doi A, Hirakata H, et al. Revival of effective and safe high-dose mizoribine for the kidney transplantation. Clin Transplant 2006;20:590–5.

[5] European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. Lancet 1995;345:1321–5.

[6] Zhang X, Fu SX, Han S, Zheng XY, Wang LM. The argument for the use of mizoribine in renal transplantation: a meta-analysis and systemic review. Transpl Immunol 2013;28:106–11.

[7] Simon RK, Russell NK, Barcena L, Peter JM. Mycophenolate Mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review. Transplantation 2009;87:785–94.

[8] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.

[9] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The New castle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [serial online]. Accessed January 1, 2008. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[10] Yoshimura N, Ushigome H, Nobori S, Suzuki T, Sakai K, Koshino K, et al. Excellent results of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroids in renal transplant recipients—4 year results. Transplant Proc 2013;45:1472–5.

[11] Oshiro Y, Nakagawa K, Hoshinaga K, Aikawa A, Shishido S, Yoshida K, et al. A Japanese multicenter study of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroid in renal transplantation. Transplant Proc 2013;45:1476–80.

[12] Sia IG, Patel R. New strategies for prevention and therapy of cytomegalovirus infection and disease in solid-organ transplant recipients. CMR 2000;13:83–121.

[13] Takashi K, Tohru D, Yoshihiro Y, Takemoto M, Oshima K, Eizuru Y, et al. Novel anticytomegalovirus activity of immunosuppressant mizoribine and its synergism with ganciclovir. JPET 2010;333:816–21.

[14] Zhan SL, Cai M, Shi BY, Li ZL, Wei X, Wang S. Large-dose mizoribine in combination with cyclosporine prevents cytomegalovirus infection after kidney transplantation: a randomized controlled study. CRTER 2008;12:878–80.

[15] Zhang LY, Yao XF, Xue Q, Fan YH. Effective evaluation of mizoribine in the early period after renal transplantation. CRTER 2007;11:3134–5.

[16] Liu B, Zeng FJ, Ming CS, Lin ZB. Prospective trial of Mizoribine versus Mycophenolate mofetil in Cyclosporine-based kidney transplantation. China J Modern Med 2006;16:2629–31.

[17] Han S, Lien B, Fan Y, Zhu YH. Comparison of mizoribine with mycophenolate mofetil in triple immunosuppressive therapy in patients with renal transplantation. China J New Drugs 2010;19:595–8.

[18] Ming AM, Lin MZ, Zhao M, Yue LS, Li M, Fan LP. Application of mizoribine in cadaveric renal transplantation. J Clin Urol 2003;18:6–7.

[19] Takahara S, Takahashi K, Akiyama T, Nobori S, Suzuki T, Sakai K, et al. Randomized comparative trial of mizoribine versus mycophenolate mofetil in combination with tacrolimus for living donor renal transplantation. Clin Exp Nephrol 2013;17:899–904.

[20] Ju MK, Huh KH, Park KT, Kim SJ, Cho BH, Kim CD, et al. Mizoribine versus Mycophenolate Mofetil in combination therapy with Tacrolimus for De Novo kidney transplantation: evaluation of efficacy and safety. Transplant Proc 2013;45:1481–6.

[21] Li XC, Long CG, Meng DL, Luo WF, Wang YG, Luo LB. Application of mizoribine in living related donor kidney transplantation. Jiangxi Med J 2009;44:1162–4.

[22] Chen JS, Ji SM, Sha GZ, Chen Z, Sun QQ, Wen JQ, et al. Mizoribine: an effective and low-toxic immunosuppressant for renal transplantation patients. J Med Postgrad 2009;22:54–6.

[23] Jiang LN, Zhou HL, Gao JL, Gao BS, Fu W. Effective evaluation of mizoribine after renal transplantation. J Jilin Univ 2008;34:687–9.

[24] Han L, Li JL. Effect of anti-acute rejection with mizorbine renal transplantation. J Med Forum 2005;26:10–1.

[25] Ohashi Y, Okazakil H, Sato T, Amada N, Kikuchi H, Yamaguchi M. A random trial of mizoribine versus mycophenolate mofetil in tacrolimus-based renal transplantation. Transplantation 2004;78:660.

[26] Ding X, Zhu X, Zhang Y, Zhang L, Cheng M, Yu Y, et al. Influence of serum uric acid levels in response to the conversion from mycophenolate mofetil to mizoribine in kidney transplant recipients. Transplant Proc 2013;45:190–3.

[27] Yoshimura N, Ushigome H, Akioka K, Nobori S, Suzuki T, Sakai K, et al. The beneficial effect of high-dose mizoribine combined with cyclosporine, basiliximab, and corticosteroids on CMV infection in renal transplant recipients. Clin Exp Nephrol 2013;17:127–33.

[28] Yoshimura N, Ushigome H, Matsuyama M, Nobori S, Suzuki T, Sakai K, et al. The efficacy and safety of high-dose mizoribine in ABO-incompatible kidney transplantation using anti-CD20 and anti-CD25 antibody without splenectomy treatment. Transplant Proc 2012;44:140–3.

[29] Nakamura N, Mikami H, Matsuoka H, Irie S, Abe Y, Sasatomi Y, et al. Experiences of high-dose mizoribine as antimetabolite immunosuppressants for kidney transplantation. Transplant Proc 2012;44:150–3.