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Review

The argument for the use of mizoribine in renal transplantation: A meta-analysis and systemic review

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ABSTRACT

Objective: The aim of this study is to evaluate the efficacy and safety of mizoribine (MZR) for immunosuppressive therapy in renal transplantation.
Methods: A systematic search of the eligible studies that compared MZR with azathioprine (AZA) for post renal transplant immunosuppressive therapy was performed by using MEDLINE, EMBASE, and the Cochrane Library. Meta-analyses were performed to study the pooled effects of relative risk (RR) and weighted mean difference with 95% confidence intervals (CI).
Results: A total of 486 participants from seven clinical trials were included. MZR demonstrated comparable efficacy in terms of acute rejection, patient/graft survival, and serum creatinine. However, MZR was associated with a significantly lower incidence of adverse events as compared with AZA (RR 0.39, CI 0.21–0.73, $p = 0.003$). Specifically, recipients receiving MZR suffered from significantly fewer episodes of myelosuppression (RR 0.12, CI 0.02–0.54, $p = 0.006$) and leukopenia (RR 0.20, CI 0.06–0.70, $p = 0.01$). Also, MZR seemed to offer more favorable outcomes in terms of hepatic dysfunction, infection and diabetes, although the differences were not statistically significant.
Conclusions: MZR is a safe, well-tolerated and effective immunosuppressive agent that can be recommended as an alternative to AZA in renal transplant recipients, although further studies are needed to balance its effect with mycophenolate mofetil.

Contents

Abbreviations: AZA, (azathioprine); MMF, (mycophenolate mofetil); MZR, (mizoribine); CsA, (cyclosporine); AR, (acute rejection); RR, (relative risk); CI, (confidence intervals); CMV, (cytomegalovirus); BKV, (polyomavirus).

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1. Introduction

Azathioprine (AZA) is a purine analog and has been widely adopted as a maintenance immunosuppressive agent in renal transplant recipients before the advent of mycophenolate mofetil (MMF) [1,2]. However, AZA is associated with a series of adverse events even at relatively low doses, predominantly including myelosuppression [3] and hepatic dysfunction [4], which significantly limits its clinical use.

Mizoribine (MZR) is a nucleoside of the imidazole class and is known to inhibit the de novo biosynthesis of purines in an alternative way to AZA [5]. MZR was found to suppress both humoral and cellular immunity by selectively inhibiting lymphocyte proliferation, and has been approved for use in the prevention of rejection following renal transplantation in Japan since 1984 [6,7]. Previous studies have revealed that MZR could serve as a viable alternative for AZA in kidney transplant recipients with hepatic dysfunction and/or agranulocytosis [8,9]. Thereafter, a number of clinical trials have been performed to evaluate the efficacy and safety profile of MZR. However, the results from these trials varied among one another, making it difficult to reach consensus on its application. We therefore conduct a meta-analysis to compare the safety and efficacy of MZR with AZA, in order to provide objective information that may help guide transplant physicians.

2. Methods

2.1. Trial selection

Published and unpublished trials that fulfilled the following selection criteria were included in the present meta-analysis: 1) study design: prospective clinical trials; 2) population: adult renal transplant recipients, from both deceased and living donors, devoid of those receiving multi-organ transplantation; and 3) intervention: MZR versus AZA as immunosuppressive agents following renal transplantation. To minimize publication bias, we did not limit the publication language.

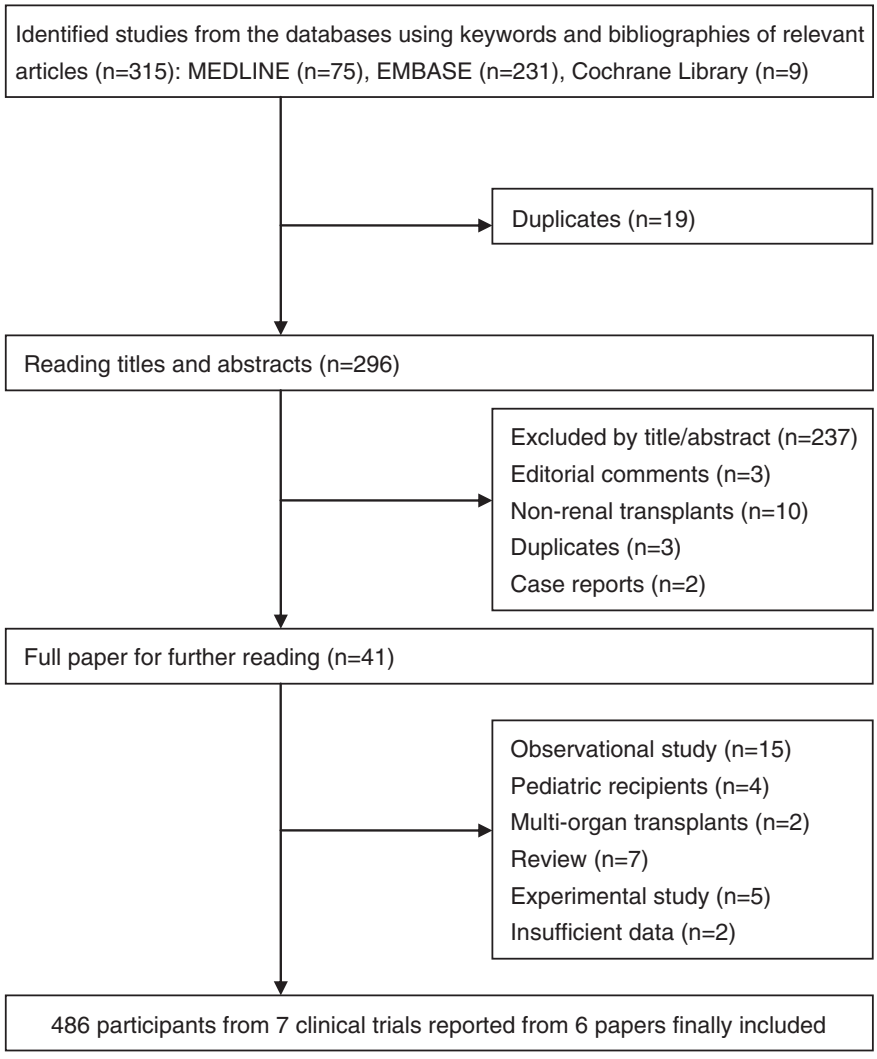

Fig. 1. Flow of studies through the review process.

Table 1
Characteristics of included studies.

Studies	No. (MZR/AZA)	Intervention arm			Control arm			Follow-up (M)
		Regimen	Dose (mg/kg/day) or target level (ng/ml)		Regimen	Dose (mg/kg/day) or target level (ng/ml)		
			Initial	Maintenance		Initial	Maintenance	
Cho (2001) [13]	93 (51/42)	MZ ± CyA + St	3 mg/kg/day	3 mg/kg/day	AZA ± CyA + St	NS	NS	24
Tanabe (1999) [14]	116 (58/58)	MZ + CyA + St	4–5 mg/kg/day	4–5 mg/kg/day	AZA + CyA + St	2 mg/kg/day	1 mg/kg/day	108
Lee (1995) (I) [12]	40 (20/20)	MZ + CyA + St	3 mg/kg/day	3 mg/kg/day	AZA + CyA + St	2 mg/kg/day	2 mg/kg/day	36
Lee (1995) (II) [12]	37 (20/17)	MZ + CyA + St	3 mg/kg/day	3 mg/kg/day	AZA + CyA + St	2 mg/kg/day	2 mg/kg/day	6
Mita (1990) [15]	61 (48/13)	MZ + CyA + St	2 mg/kg/day	2 mg/kg/day	AZA + CyA + St	1 mg/kg/day	1 mg/kg/day	36
Kokado (1989) [16]	30 (19/11)	MZ + CyA + St	2.5 mg/kg/day	5 mg/kg/day	AZA + CyA + St	1–2 mg/kg/day	NS	12
Aso (1987) [17]	109 (23/86)	MZ + CyA + St	2 mg/kg/day	NS	AZA + CyA + St	NS	NS	12

MZR, mizoribine; AZA, azathioprine; NS, not specified.

2.2. Literature search

We searched databases including MEDLINE, EMBASE and Cochrane Library to identify pertinent citations published since January 1979. The following searching strategies were employed: (renal transplant* [Text Word] OR kidney transplant*[Text Word]) AND (mizoribine [Text Word] OR bredinin [Text Word] OR MZR [Text Word]) AND (Imuran [Text Word] OR azathioprine [Text Word] OR AZA [Text Word]). For the unpublished data, we searched trial registries including clinicaltrial.gov, the national research register and current controlled trials. A manual search was performed by checking the reference lists in recent important publications and abstracts from international congresses of the Transplantation Society and those published in Transplantation, American Journal of Transplantation or Clinical Transplantation. We also reviewed the bibliographies from citations for related articles. Manufacturers of relevant pharmaceutical agents were contacted for additional materials.

2.3. Data extraction

Data extraction and analysis were carried out independently by two reviewers (X. Zhang and S.X. Fu) by using a pre-designed form. Data were extracted by a digitizing software-Engauge Digitizer (version 4.1; free software downloaded from http://sourceforge.net) from the chart if the raw data were not displayed. For results not clearly described in the paper, the author was contacted for the necessary data. Disagreements were resolved by discussion. In this meta-analysis, the efficacy variables included acute rejection (AR), patient death, graft loss, and serum creatinine. The safety variables included myelosuppression, leukopenia, hepatic dysfunction, infection, and diabetes.

2.4. Quality assessment

Two reviewers (X. Zhang and S.X. Fu) used standard criteria (e.g., allocation concealment, blinding, intention-to-treat analysis, and withdrawals) to assess the study quality, in addition to quantitative quality assessment by using the scoring system developed by Jadad et al. [10]. The quality scoring system was as follows: 1) allocation concealment, coded as adequate (1 score), or inadequate or unclear (0 score); 2) blinding, coded as double blind (2 scores), single blind (1 score), or open label (0 score); 3) intention-to-treat analysis, coded as used (1 score), or not used or unable to assess (0 score); and 4) withdrawals, coded as given (1 score) and not given (0 score).

2.5. Statistical analysis

An estimate of the relative risk (RR) was used for dichotomous outcomes. Results were reported with 95% confidence intervals (CIs) on the test for the overall effect, and heterogeneity was quantified by using a chi-square test with a p value <0.1 considered statistically significant. For outcomes without heterogeneity, pooled effects were calculated through the fixed effect model; a randomized effect model was employed if heterogeneity was detected among studies. Review Manager (Version 5.0) was used for statistical analysis.

3. Results

3.1. Descriptions of studies

A total of 315 citations were initially identified, of which nineteen duplicated articles were excluded. Forty-one papers were retrieved for full-text review after excluding 255 articles on the basis of titles and abstracts. Data from one original publication [11] included in this meta-analysis were updated by subsequent full papers with a longer observational follow-up [12]. Additionally, as the results from two separate trials (both of which met the inclusion criteria) were reported in the same publication by Lee et al. [12], we included both of them and labeled with Lee (1995) (I) and Lee (1995) (II) in this paper. Finally, seven clinical trials involving 486 participants were included in the analysis [12–17]. The specific flowchart of identifying qualified studies is shown in Fig. 1. Demographics of the studies, including specific immunosuppressive regimens and follow-ups, are shown in Table 1. Quality assessments of the studies are shown in Table 2.

3.2. Efficacy profiles

3.2.1. Acute rejection

Incidences of AR were reported in five studies. Pooled results failed to demonstrate statistically significant differences between MZR and AZA groups under homogenous conditions (Fig. 2A).

3.2.2. Patient survival

Patient death was reported in four studies but such events occurred in only two studies, and there was no significant difference between the two groups (Fig. 2B). No heterogeneity was detected.

3.2.3. Graft survival

Incidences of graft loss were reported in all seven trials. Patients receiving MZR seemed to have higher graft survival rates compared to those with AZA treatment, although such difference did not reach statistical significance (Fig. 2C). The heterogeneity was absent.

3.2.4. Graft function

Similar results were yielded with respect to serum creatinine (Fig. 2D). The heterogeneity was high ($I^2 = 87\%$), but completely disappeared only when the study by Kokado et al. was excluded from the analysis, suggesting that varied doses of MZR and CsA use may partially explain the heterogeneity among studies.

Table 2
Quality assessment of studies included.

Studies	AC	Blinding	ITT	Withdrawals	Score
Cho (2001) [13]	Unclear	Open-label	Yes	NS	1
Tanabe (1999) [14]	Unclear	NS	No	27.6%	1
Lee (1995) (I) [12]	Unclear	Open-label	No	25.0%	1
Lee (1995) (II) [12]	Unclear	Open-label	No	NS	0
Mita (1990) [15]	Unclear	NS	No	0.0%	1
Kokado (1989) [16]	Unclear	NS	No	60.0%	1
Aso (1987) [17]	Unclear	NS	No	42.2%	1

AC, allocation concealment; ITT, intention-to-treat.

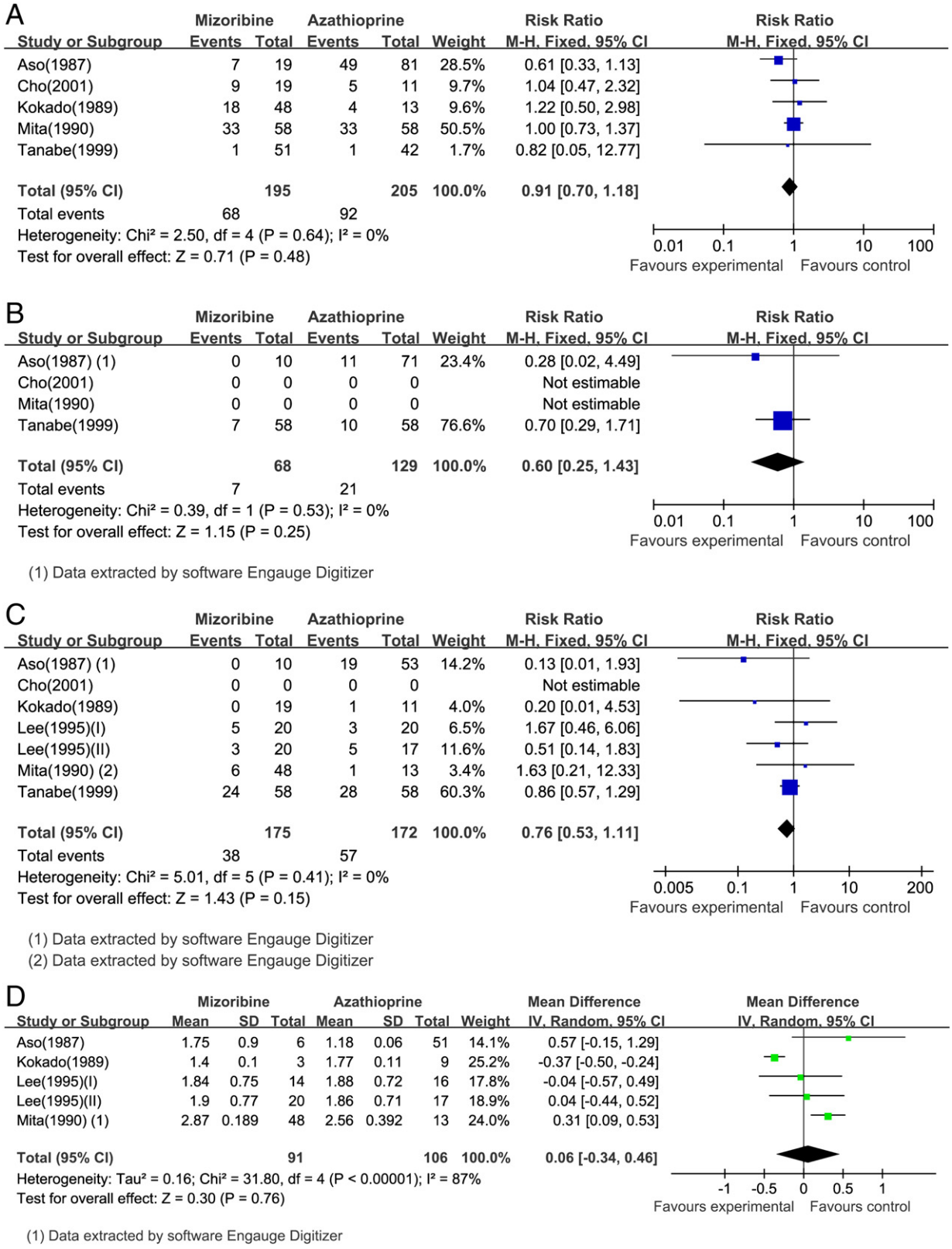

Fig. 2. Forest plot to show the efficacy profile of MZR. Pooled estimates of AR rate (A), patient survival (B), graft survival (C), and serum creatinine comparing MZR with AZA.

3.3. Safety profiles

The safety profile of MZR was evaluated by the measurement of adverse events, including myelosuppression, leukopenia, hepatic dysfunction, infection, and diabetes. Overall, the MZR group had a significant lower incidence of adverse events compared to the AZA group with high heterogeneity detected (Fig. 3). The maintenance dose of MZR may contribute to the heterogeneity. In the analysis of specific variables, it was noted that patients receiving MZR had statistically significant fewer episodes of myelosuppression and leukopenia (Fig. 3). Also, MZR seemed to offer more favorable outcomes in terms of hepatic dysfunction, infection and diabetes, although the differences failed to reach a statistical significance (Fig. 3).

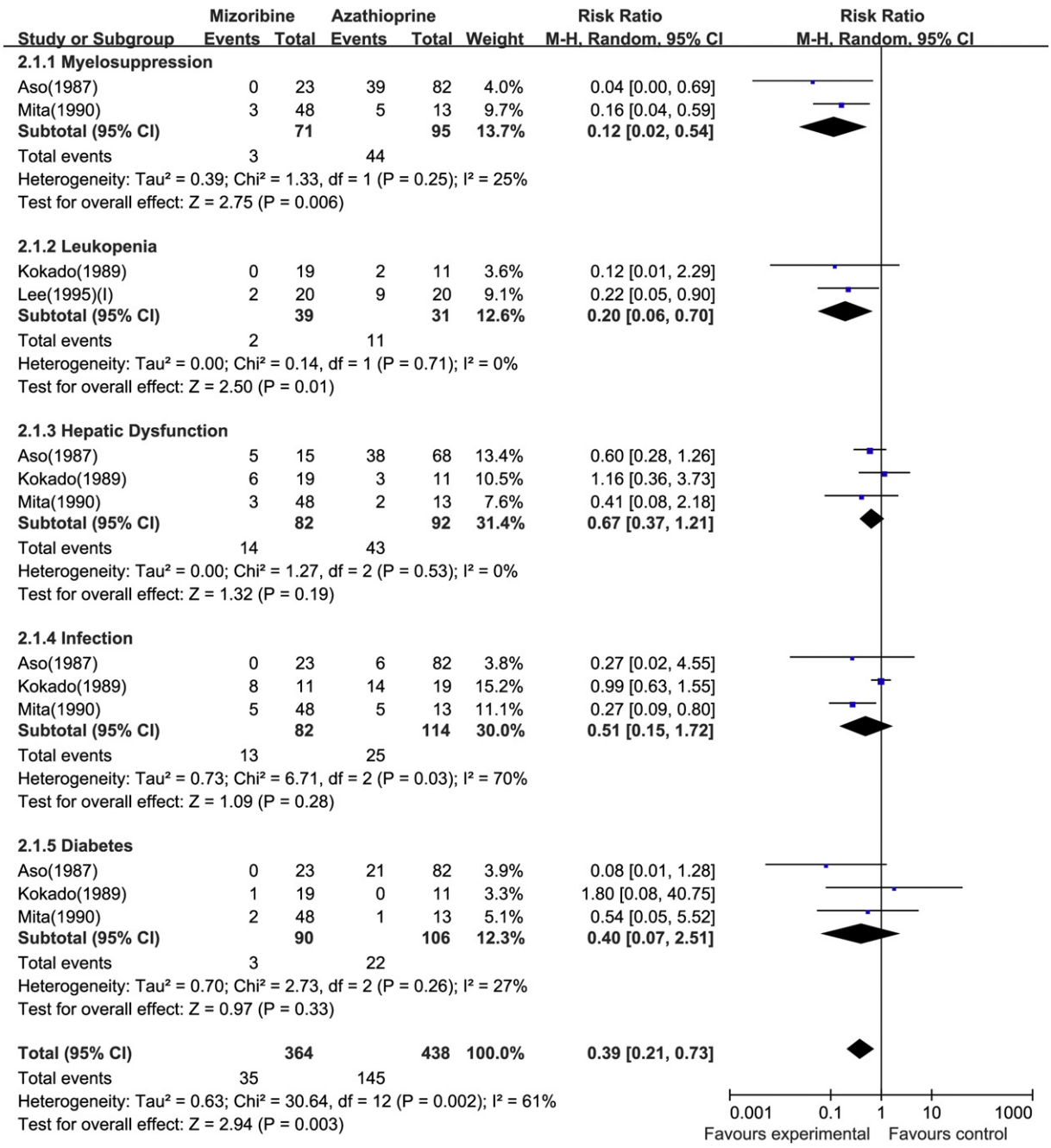

Fig. 3. Forest plot to show the safety profile of MZR. Pooled estimates of myelosuppression, leukopenia, hepatic dysfunction, infection, and diabetes comparing MZR with AZA.

4. Discussion

MZR has been approved in Japan for both induction and maintenance of immunosuppressive therapy in post renal transplant recipients since about 30 years ago [8,9]. As MZR is considered less potent for immunosuppression [18], it has not been used widely worldwide, although it has also been released in China and South Korea since 1999. The present meta-analysis showed that MZR seems generally superior to AZA in the safety profile, and is as effective as AZA with respect to the AR incidence and patient/graft survival.

There are controversies over the choice of antimetabolite agents [19–21]. In the past decades, MMF has gained an increasing acceptance as a maintenance immunosuppressive medication for its excellent effect on rejection and short-term graft outcomes [22]. However, with the advent of various potent immunosuppressive agents, the main focus of renal transplantation has shifted from management of AR to long-term patient/graft survival and the quality of life of the recipients [23,24]. A 15-year follow-up study indicates that MMF failed to show overt superiority over AZA in renal transplant recipients regarding long-term outcomes [25]. At the same time, the use of MMF is known to be associated with cytomegalovirus (CMV) infection and BK virus-associated nephropathy [26], the main factors contributing to graft loss and/or death with graft function for transplant recipients [23,27]. Data from this meta-analysis indicate that MZR might be a viable substitute as the maintenance antimetabolite agent in renal transplantation.

Given that MZR is directly excreted through the kidney, its dosage should be adjusted appropriately based on the improved renal function [28]. The standard dose of MZR in the 1990s used to be 1–3 mg/kg/day, with the therapeutic serum trough concentration ranging between 0.1

and 3 μg/ml, in a triple-therapy protocol with cyclosporine (CsA) and steroids [8,29]. However, to compensate for its relatively less potent immunosuppressive effect, some transplant centers have recommended high doses of MZR (≥5 mg/kg/day) [30]. It was reported that high-dose (6 mg/kg/day) MZR with CsA, basiliximab, and steroids could achieve satisfactory immunosuppression with a lower rate of CMV and BK virus-associated events as compared with MMF [31,32]. However, considering the varying immunologic conditions of transplant recipients, we suggest that great attention should be paid to individualized therapy, and further clinical trials are still warranted to establish the optimal dosage and serum trough level of MZR.

Medical cost is another consideration in the selection of an immunosuppressive agent. Especially under the condition of comparable efficacy, medical expense may be a deciding factor in choosing a therapeutic regimen. Although none of the included trials in this meta-analysis reported the medical cost, a study by Sugitani et al. [33] indicates that MZR has a better cost-effectiveness compared with MMF during the maintenance phase after renal transplantation. Therefore, this can serve as an additional argument for a positive recommendation for the use of MZR.

Some limitations within the present meta-analysis deserve to be noted: (i) The mean follow-up durations of the included trials is relatively short. Given that a long time length might be needed for the superiority of MZR to translate into better graft/patient outcomes, we may underestimate the benefit of MZR in this study. (ii) The study quality of the included trials is relatively low, which might limit the ability to reach convincing conclusions. (iii) All the included studies were conducted among Asian populations, and no data derived from Caucasians or black people are available, which makes it difficult to extend our conclusions to all recipients. (iv) All the trials were conducted before the widespread use of tacrolimus and antibody induction therapy, and therefore further studies may still be needed to elucidate its effect under the current immunosuppressive protocols. (v) Because of the limited number of studies available, the analysis did not assess the efficacy and safety of MZR in specific patient populations, such as live versus deceased donors, first graft versus secondary graft, or low-versus high-risk recipients.

The findings obtained from this meta-analysis provide evidence for the efficacy and safety of MZR use in renal transplant recipients. We suggest that more large-sample clinical trials with stricter design and longer follow-ups be conducted to evaluate long-term efficacy of MZR versus AZA, and MMF in particular so as to finally establish the optimal immunosuppressive protocol in renal transplantation.

Acknowledgments

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