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Comparison Between Mycophenolate Mofetil and Azathioprine for Preventing Renal Relapse in Lupus Nephritis: An Evidence-based Case Report

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ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease which involved many organs. One of its severe manifestations is lupus nephritis (LN). Treatment of LN consists of two phases, induction and maintenance. Inappropriate treatment approach could increase morbidity and mortality in LN patients. Renal flare is among many bad outcomes of LN that should be mitigated with an appropriate therapeutic approach. Various guidelines stated usage of mycophenolate mofetil (MMF) or azathioprine (AZA) as an appropriate immunosuppresant in the maintenance phase. However, it is not clear which agent acts best in preventing renal flare. This paper presents a case of 21 years old SLE female patient with history of renal flare 1 month prior to admission. This study aimed to give evidence-based recommendation to adjust this patient's therapy in order to prevent future renal flare episode. **Method:** Literature search was done on four online databases, namely PubMed, EBSCO, Cohrane Library, and ProQuest. Articles with randomized clinical trial (RCT), systematic review and meta-analysis study design were retrieved and selected based on inclusion and exclusion criterias. Critical appraisal was done using appraisal sheet provided by Oxford Centre of Evidence-based Medicine. Articles were appraised based on its validity, importance, and applicability. **Results:** There were 144 articles retrieved from literature searching. Further screening and *full-text* reading yields to 2 RCTs and 2 meta-analysis that were critically appraised. Both meta-analysis were satisfactory on their validity, while none of RCTs found were blinded studies. Both meta-analyses showed pooled risk ratio (RR) of 0.70 (0.49 – 1.00) for renal flare outcome in the use of mycophenolate mofetil compared to azathioprine. **Conclusion**: There are no significant differences between mycophenolate mofetil and azathioprine in prevention of renal flare. Based on applicability, azathioprine is more appropriate to be given in this patient, in accordance to her background.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disorder which involved many organs. Lupus nephritis (LN) is one of its most severe complications. It is estimated that 60% of adult patients with SLE had this condition.[1] Lupus nephritis has various severity grades. There was a classification system proposed by World Health Organization (WHO) which divides LN into six different classes based on histological and complex immune location properties, starting from mild mesangial proliferations to severe endothelial proliferations which may progress to sclerotic glomerular disease. A new classification is proposed by International Society of Nephrologist and Renal Pathology Society (ISN/RPS) to renew this classification by adding the categories of focal lesion, diffused, active, inactive, or chronic.[2] Renal involvement in SLE without appropriate treatment will lead to progressive deterioration of renal function, which in turns will increase morbidity and mortality. Inappropriate treatment may lead to undesirable

outcomes such as End-Stage Renal Disease (ESRD) and even death.[3] Therefore, main goal of LN treatment is to control the progression of disease itself in order to maintain normal renal function and prevent its deterioriation.

Treatment of moderate/severe LN consists of induction phase continued by maintenance phase.[4] Generally, high dose corticosteroid and cyclophosphamides (CYC) are given during induction phase. As CYC may cause a number of severe adverse effects, including malignancy, therapeutic agents used during maintenance phase is alternated into low dose corticosteroid combined with immunosuppresant agent which is either mycophenolate mofetil (MMF) or azathioprine (AZA).[5]

During maintenance, control of the symptoms with the lowest dosage possible that still prevent undesirable outcomes is preferable.

Alongside ESRD or mortality, one of the bad outcomes of LN is renal relapse or renal flare. According to European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) in their recommendation[6], renal flare is defined as (i) nephritic flare, marked by increases serum creatinin by ≥30% (or decrease of GFR by ≥10%) with active urinary sediments and glomerular hematuria with ≥10 cells per high power field; and (ii) proteinuric flare, which is double in urine protein: creatinine ratio >100 mg/mmol following total remission or >200 mg/mmol after partial remission. Nephritic flare affected the kidney worse than proteinuric flare.[6]

American College of Rheumatology (ACR) recommends AZA with target dose of 2 mg/kg/day or MMF with target dose of 2 g/day as immunosuppressant of choice in maintenance phase.[5] However, none stated which one is the first choice among these two. Recommendation by Indonesian Rheumatology Association (IRA)[4] also recommends either one of the two choices, with no preference of which one is better in preventing renal flare and other outcomes. Therefore, this article aimed to compare MMF and AZA for maintenance therapy of LN in preventing renal relapse.

Case Ilustration

Female, 21 years old, 40 kg, came to emergency department of Persahabatan Hospital with main complaint of ulcerations on both her feet for 7 days before admission. Patient started to feel fatigue also 7 days prior to admission, pustule-like lesions also started to appear in her abdomen, chest, and upper part of her both lower extremities. The lesions burst and excrete bloods and pus 1 day before admission, so patients came to emergency department of Persahabatan Hospital. In the emergency unit, blood examination revealed her haemoglobin (Hb) level was 4.2 g/dL, so she got admitted after 500 mL *packed red cells* (PRC) transfusion. Patient has been diagnosed with SLE for 3 years, manifesting with frequent oral ulcers, photosensitivity, joint tenderness, and renal involvement. Previously, patient had methylprednisolone (MP) 1x8 mg and azathioprine 1x50 mg was added 1 year later. She had a recent history of hospital admission 1 month ago due to massive edema all over her body and had previous regiment replaced with higher dose of MP 32 mg/day. Physical examination revealed dried skin, there were multiple dried ulcers on chest, abdomen, and lower limbs regions. Conjunctiva was pale, no oral ulcer. There is bilateral lower limb edema. Laboratory examination showed anemia, hypokalemia, and hypoalbuminemia. Initial laboratory analysis during admission revealed serum creatinine 1.3 mg/dL and serum albumin 1.8 g/dL.

The patient was then admitted with the following problems: SLE with haematology, mucocutaneous, and renal involvement, multiple ulcerations on lower limbs, abdomen, and chest considered to be vasculitis with secondary infection, hypokalemia, and hypoalbuminemia. Patient was planned to undergo electrolyte, ureum/creatinine, albumin, urinary, and microalbuminuria follow-up examination. Patient was treated with high protein diet, K-N2 intravenous fluid drainage 500 ml every 8 hours, meropenem 3 x 1 g IV, methylprednisolone 16-8-8 mg, and potassium

chloride 3x1200 mg. After 7 days of admission, she was planned to be discharged. Considering her history of renal relapse after maintenance therapy with azathioprine 1x50 mg and methylprednisolone 1x8 mg, we consider to alter her maintenance therapy in order to prevent future incident of renal flare.

2. Research Methods

Based on the case, we arranged clinical question as follows: "*In patients with lupus nephritis, is mycophonelate mofetil, compared to azathioprine, more effective in preventing renal flare?*"

To answer the question, literature search was done on four large electronic databases. Search on PubMed, EBSCO, Cochrane Library, and ProQuest was done with "lupus nephritis", mycophenolate mofetil", "azathioprine", "renal flare", and their synonyms. Literature search was done on November 15th 2017.

During our literature search, we included Randomized Controlled Trials (RCTs), systematic review, and meta-analysis studies written in English or Indonesian. The articles included were published no earlier than January 1st, 2013. Articles with no available full-text were excluded. Our search within these limitations yielded 59 articles for title/abstract screening. Screening resulted in 12 articles, duplicate removal leaving 6 of them for full-text reading. Further reading yielded4 useful articles to be critically appraised using appraisal sheet from Center of Evidence-based Medicine, University of Oxford.[7] Details of the search process is depicted in **Figure 1**. We determined Level of Evidence of the articles based on criteria also published by Oxford Center of Evidence-based Medicine.[8] Critical appraisal was done based on validity, importance, and applicability analysis.

3. Results

Results of critical appraisal is summarized in **Table 1** and **Table 2.**

Apart of blinding, validities of both RCTs were satisfactory. Although we couldn't find statements regarding characteristics of the subjects in the long-term follow up report of Tamirou et al[10], a look in their original publication[13] revealed similarities between the two groups. Tamirou et al did not explicitly state whether they utilized blinding, while Kaballo et al[9] explained clearly that their study design was an open-label study. Both meta-analysis from Feng et al[11] and Maneiro et al[12] were valid with Level of Evidence of IA. Both Feng and Maneiro used Jadad score[14] to assess the quality of RCTs included in their studies, and all RCTs included in the analysis scored 2−4 or 3−5, which considered as having good quality.

While importance of both RCTs were determined by numbers shown in **Table 1,** importance analysis of meta-analysis studies by Feng et al and Maneiro et al were determined by observing *forest plot* shown in the study. There were four RCTs included in meta-analysis of both Feng et al and Maneiro et al, all of which were the same studies. Therefore, this study only analyzed forest plot shown by Feng et al in his study, which was identical with that of Maneiro et al, as shown in **Figure 2.**

There is no significant heterogeneity from these four studies, as demonstrated with I^2 = 0% (< 40%). An eyeball test on the forest plot supports this statement. Pooled risk ratio seems to favor MMF even though it does not reach statistical significance with relative risk (RR) 0.70 (0.49 – 1.00, 95% CI).

Figure 1. Literature Search Process

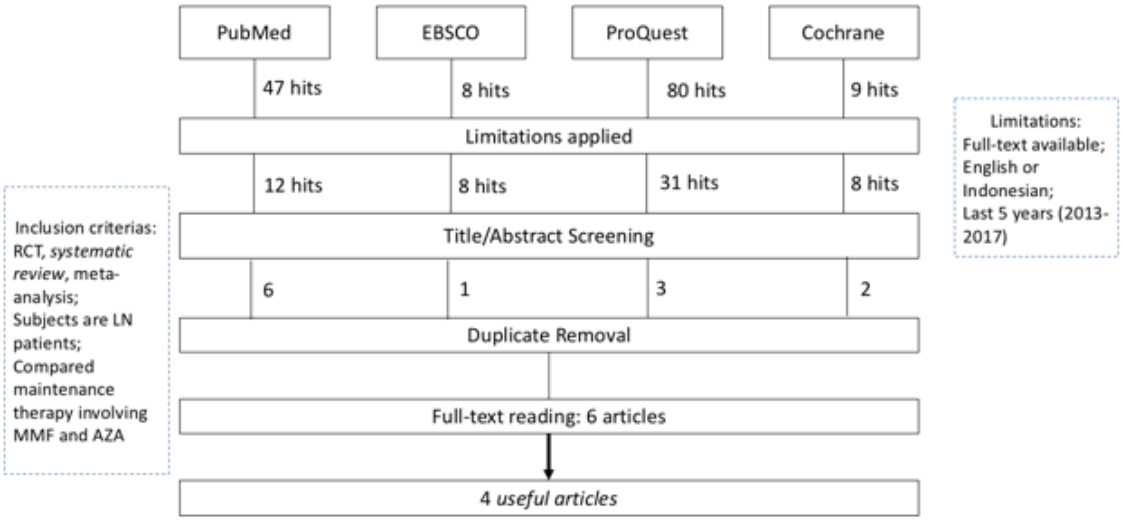


Table 1. Critical appraisal of RCT studies

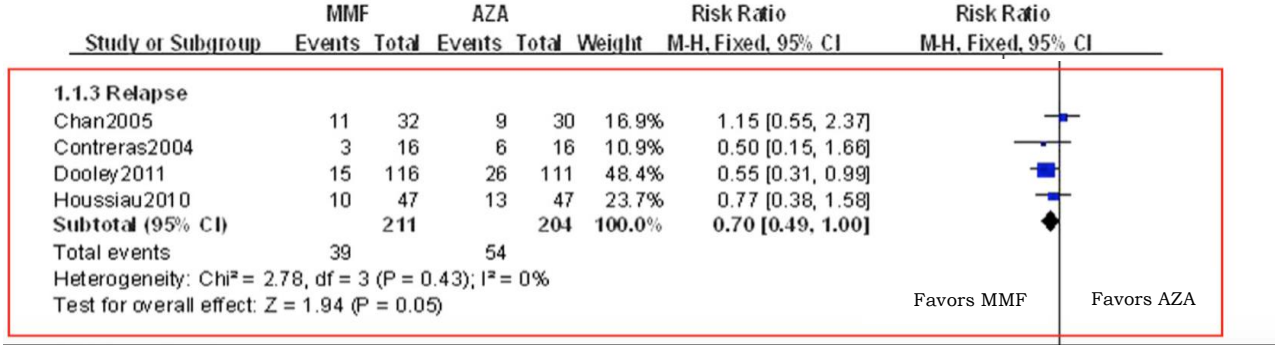
Article	Validity					Importance						Applicability		
	Randomization	Similarity between two groups	Equally treated	Intention-to-treat analysis	Blinding	CER	EER	RR	RRR	ARR	NNT	Similarity of study and case	Values and preferences of patient	*Level of Evidence*
Kaballo et al[9]	+	+	+	?	-	10.0 %	9.8%	0.97 6	2.4%	0.2%	410	+	+	2B
Tamirou et al[10]	+	+	+	+	?	42.3 %	35.8 %	0.84 7	15.3 %	6.5%	16	+	+	2B

CER, *control event rate*; EER, *experimental event rate*; RR, *relative risk*; RRR, *relative risk reduction*; ARR, *absolute risk reduction*; NNT, *number needed to treat.*

Table 2. Critical appraisal of Meta-analysis

Article	Validity					Importance	Applicability		
	Focused question	Search strategy	Design and selection criteria of the study	Quality of studies	Results similarity		Similarity of study and case	Values and preferences of patient	*Level of Evidence*
Feng et al[11]	+	+	+	+	+	(*assessed with Forest Plot*)	+	+	1A
Maneiro et al[12]	+	+	+	+	+		+	+	1A

Figure 2. *Forest plot* on renal flare outcome from Feng et al's study. Left: favors MMF, right: favors AZA



4. DISCUSSION

Two RCTs critically appraised were both valid on their methods, even though they were not double-blinded studies. Even though this affect their scores on validity, we considered this to be tolerable, as the outcome measured in our article, renal flare, could be objectively measured, thus double-blinding is not of utmost importance. Similarly, on both meta-analysis we appraised, only 1 out of 4 RCTs included in the study was done with double-blinding. The other three were open-label studies.

As shown in **Table 1**, usage of MMF in both RCTs resulting in RR < 1 which tends to favor its usage in order to prevent renal flare. However, statistical analysis of Kaballo et al resulted in p = 0.63, while Tamirou et al which had 'time-to-renal-flare' as primary outcome of his study demonstrated hazard ratio of 1.22 (0.66 – 2.25 95% CI, p = 0.531). Both did not reach statistical significance. Our calculations shown in table 1 also demonstrate high value of number needed to treat (NNT) in both studies, which is 410 and 16 for the study of Kaballo et al and Tamirou et al, respectively. This supports that there are no significant differences, because to prevent renal flare to only one, hundreds must be involved in altering therapy.

Study by Feng et al and Maneiro et al supports this statement. Pooled RR of 0.70 with 95% CI ranges from 0.49 – 1.00 touches the *line of no effect*, which is 1.00. In addition, three out of four studies involved in the analysis showed RR with confidence interval that crosses this line of no effect. Based on that, we concluded that results of meta-analysis study also showed no significant differences for renal flare outcome in the use of MMF or AZA.

This report has some limitations. First, definition of *renal flare* itself differs among studies. Tamirou et al defined renal flare as (1) proteinuric flare, which is development of nephrotic syndrome or three-fold increase of 24h proteinuria in 3 months period for those with low-grade baseline proteinuria (0.5−1 g); or (2) nephritic flare, a ≥33% increases in serum creatinine within a 1-month period directly attributed to lupus and confirmed. Meanwhile, Kaballo et al defined flare as (1) proteinuric flare: increase in 24h proteinuria of > 2 g for patients with basal proteinuria of > 3 g, or doubled 24h proteinuria value for other patients; or (2) nephritic flare: increase of serum creatinine ≥50% with urinary nephritic sediments. Cut-off values in proteinuria or serum creatinine in these 2 studies were clearly different. RCTs involved in meta-analysis also had these differences. One study by Houssiau et al[13] had a similar definition with Tamirou et al's study, while other studies had different cut-off values. One study even defined relapse only by clinical judgment, which includes need of increased steroid dose.[15]

Second, methods of induction therapy were also different among studies. Kaballo et al gave pulse dose cyclophosphamide IV (500 mg/m^2, 500 mg max) monthly for 6 months plus 3 consecutive pulses of methylprednisolone IV (15 mg/kg/day, max 500 mg) as induction therapy, while Tamirou et al used pulse dose methylprednisolone IV 750 mg/day for 3 days plus 6 times single-dose 500 mg cyclophosphamide given in the first 10 weeks. In studies analyzed by Feng et al, 2 studies gave another regiments for induction, one of them uses MMF in induction therapy. These differences could potentially cause bias in the results. However, one RCT analysed in study of Feng et al stated that MMF and cyclophosphamide as induction therapy showed consistent result regardless of the induction therapy, so potential bias caused by different induction therapy regiments could be reduced.

Third, dosage of MMF or AZA for maintenance therapy also had its differences. Tamirou et al gave MMF with target dose of 2 g/day and AZA with target dose 2 mg/kg/day. Kaballo et al used similar dose for AZA, but MMF target dose were specified for 22 mg/kg/day with dose ranged from 1 to 3 g/day. On the other hand, RCTs in the meta-analysis also used different doses. Two studies used MMF dose of 2 g/day, one targeted 1 g/day, while the other 0.5−3 g/day. As for AZA, two studies used similar target dose of 2 mg/kg/day, while the other two used different dose range of 1.5−2 mg/kg/day and 1−3 mg/kg/day.[12]

These differences in renal flare definition, induction regiments, and maintenance dose are all factors that may increase heterogeneity in this report, thus introduces potential risk of bias. However, regardless of these differences, we still found consistent results regarding renal flare outcome, which showed no significant differences between these two groups of maintenance therapy. Heterogeneity analysis on the meta-analysis showed no significant heterogeneity seen on statistical perspectives with $I^2 < 40\%$.[16]

From applicability perspective, MMF tends to have less adverse effects. Two outcomes that were analysed by Feng et al regarding adverse effect, which is leukopenia and amenorrhea, both favors MMF with significant reduced adverse event. However, MMF is not suitable to be consumed during pregnancy for its teratogenic effect.[17] This has to be considered while treating woman with child-bearing age, such as this patient. Today, MMF is still more expensive, with prominent price different reaching to ten times more expensive than AZA.[11,13] With no significant differences in preventing renal flare between MMF and AZA, we did not recommend change in maintenance therapy for this patient. One thing to be noted though, is the dosage of AZA received by this patient. Weighted 40 kg, this patient received AZA of only 50 mg/day, which is only 1.2 mg/kg/day. Meanwhile, most studies targeted AZA dose to 2 mg/kg/day. Therefore, we recommend dose of AZA to be adjusted in this patient

5. CONCLUSION

Based on the results, we can conclude that there are no significant differences between MMF and AZA for maintenance therapy of LN in preventing renal flare. On applicability analysis, MMF had less adverse effects,

but cost perspective and its teratogenic effect makes AZA a more appropriate choice for this patient. Therefore, we did not recommend alternation of maintenance therapy in this patient.

6. Recommendation

We recommend dose adjustment for AZA received by this patient to be increased to 2 mg/kg/day for a more optimum effect. Meta-analysis with less heterogeneity may be needed to better demonstrate differences between AZA and MMF as maintenance therapy.

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