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Research Article

STUDY ON EFFECTIVENESS AND SIDE EFFECT OF MYCOPHENOLATE MOFETIL VERSUS AZATHIOPRINE IN MAINTENANCE TREATMENT OF LUPUS NEPHRITIS

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ABSTRACT

Objective: This study investigated the effects of mycophenolate mofetil and azathioprine on serum creatinine, creatinine clearance and proteinurea in maintenance treatment of lupus nephritis.

Methods: This retrospective observational study was carried out in a tertiary hospital. Patients with lupus nephritis were selected as convenience sampling method based on inclusion and exclusion criteria. All the data were obtained from the patients' medical records.

Results: No significance differences were observed in mean improvement of serum creatinine, creatinine clearance and proteinurea at after one year treatment with either mycophenolate mofetil or azathioprine.

Conclusion: Our study demonstrated that mycophenolate mofetil and azathioprine had similar effectiveness in the maintenance treatment of lupus nephritis.

Keywords: Mycophenolate mofetil, Azathioprine, Lupus nephritis.

INTRODUCTION

Lupus nephritis is defined as renal involvement of an autoimmune disease Systemic Lupus Erythematosus (SLE) and it is one of the most severe manifestations of SLE [1]. Previous report showed that lupus nephritis affects both men and women; however it occurs more frequently in women [2].

The usual goals of therapy in treating lupus nephritis are to induce remission, to prevent episodes of relapse and to prevent the complications of the disease which include the progression of end-stage renal disease [3]. The treatment recommendation of lupus nephritis is based on the classification of the lupus nephritis itself [4]. According to World Health Organization (WHO) and more recently, International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, lupus nephritis can be classified from Class I to Class VI. Extensive glucocorticosteroid and immunosuppressive therapy are required in Class III and IV lupus nephritis [5-6].

Mycophenolate mofetil has been used widely in the treatment of lupus nephritis. It inhibits the formation of inosine monophosphate dehydrogenase which is required for the de novo synthesis of guanosine nucleotides and blocks the proliferation of T cells and B cells selectively [7]. An older immunosuppressant drug, azathioprine, is a purine analogue that competitively inhibits the biosynthesis of purine nucleotides and was found to reduce antibody production, prolong graft survival and reduce severity of lupus nephritis [8].

There were several clinical trials that have demonstrated the effectiveness of mycophenolate mofetil and azathioprine in reducing renal flare, delaying progression to end-stage renal disease and improvement in serum creatinine and proteinurea in patients with lupus nephritis [9-11]. Nevertheless, the data on the effect of both mycophenolate mofetil and azathioprine in our local standard care of lupus nephritis was limited. This study aimed to determine the effects of mycophenolate mofetil and azathioprine on serum creatinine, creatinine clearance and proteinurea in maintenance treatment of lupus nephritis.

METHODS

This retrospective observational study was approved by the Universiti Kebangsaan Malaysia Research Ethic Committee (UKM 1.5.3.5/244/NF-008-2013). The sampling method in this study was convenience sampling. Patient's medical record was screened from Systemic Lupus Erythematosus Clinic (SLE) and Medical Record Department in Local Medical Centre. The data of patients with lupus nephritis who were on maintenance treatment with either mycophenolate mofetil or azathioprine for one year disregarded the year of treatment were collected.

Patients were included in the study were adult patients aged 15 years old and above, diagnosed with Class III, IV or V lupus nephritis. Diagnosis was done by the physician based on World Health Organization (WHO) 1982 classification. Patients who have completed induction therapy with cyclophosphamide and were on maintenance therapy with either mycophenolate mofetil plus corticosteroid or azathioprine plus corticosteroid for duration of one year were included in this study. Patient who were pregnant during maintenance treatment, diagnosed with cancer and had history of cancer, evidence of major infection and had allergy to the study drugs were excluded.

A total of 30 patients were included in this study which 15 patients were in mycophenolate mofetil group and another 15 patients in azathioprine group. Effectiveness of both mycophenolate mofetil and azathioprine were evaluated regardless of the dosage regimen. The effectiveness of mycophenolate mofetil and azathioprine were determined by the improvement of serum creatinine, creatinine clearance and proteinurea which were the difference between post- and pre- level (after one year treatment).

The inferential analysis was done by using IBM SPSS Statistics version 21. Parametric statistical test was employed for continuous data that was normally distributed. Non-parametric statistical test, Mann-Whitney U test was used to analyse continuous data with skewed distribution. P- value of <0.05 was regarded as statistically significant. Results were expressed as either number of items (n) with percentage (%), mean with standard deviation (SD) or mean rank.

RESULTS

The baseline characteristics of the patients were presented in Table 1. There were no significant different in all baseline characteristics of patients treated with either mycophenolate mofetil or azathioprine. 90% of the total patients with lupus nephritis were female patient and it was reported previously that female is more prone to diagnosed with lupus nephritis compared to male [2]. The baseline data of serum creatinine, creatinine clearance and proteinurea level among the treatment groups showed no significant different ($p=0.452$, $p=0.545$, $p=0.159$ respectively).

Table 1: Baseline demographic characteristics of patients with lupus nephritis who received either mycophenolate or azathioprine

Characteristics	MMF (n=15)	Azathioprine (n=15)	P value
Gender			
Male	0 (0%)	3 (10%)	p=0.224
Female	15 (50%)	12 (40%)	
Age (years, mean ± SD)	32.9±1.29	40.7±1.43	p=0.072
Weight (kg, mean ± SD)	60.7±10.35	63.9±17.0	p=0.541
Race			
Malay	8 (26.7%)	6 (20%)	p=0.590
Chinese	7 (23.3%)	8 (26.7%)	
Indian	0 (0%)	1 (3.3%)	
Renal histology			
Class III	1 (3.3%)	0 (0%)	p=0.192
Class IV	3 (10%)	2 (6.7%)	
Class III, IV	2 (6.7%)	7 (23.3%)	
Class III, V	1 (3.3%)	2 (6.7%)	
Class IV, V	8 (26.7%)	4 (13.3%)	
SrCr (µmol/L, mean ± SD)	83.0±35.06	74.53±24.91	p=0.452
CrCL (ml/min, mean ± SD)	91.89±41.09	100.96±39.84	p=0.545
Proteinurea (g/L, mean rank)	17.70	13.30	p=0.159
C3 (mg/dL, mean ± SD)	83.26±45.72	92.83±38.66	p=0.541
C4 (mg/dL, mean ± SD)	16.78±9.87	20.36±9.71	p=0.327
Systolic BP (mmHg, mean ± SD)	133.4±15.35	140.53±16.47	p=0.230
Diastolic BP (mmHg, mean rank)	15.57	15.43	p=0.967
Albumin (g/L, mean rank)	12.6	18.40	p=0.069
Hemoglobin (g/dL, mean ± SD)	12.33±1.64	12.47±1.81	p=0.826
WBC count (x10^9/L, mean ± SD)	8.18±2.64	6.71±1.61	p=0.078
Platelet count (x10^9/L, mean ± SD)	242±63.56	240.87±109.42	p=0.973

P < 0.05 denotes statistical significance, mean rank for non-parametric test

Values are the number of patients (with percentage)

SrCr = serum creatinine; CrCl = creatinine clearance, C3 = complement component 3;

C4 = complement component 4

Table 2 showed the number of patients who reached the improvement on serum creatinine, creatinine clearance and proteinurea levels were not significantly different between the two treatment groups after one year of treatment (p=1.000, p=1.000, p=0.272 respectively).

Table 2: Number of patients improved on serum creatinine, creatinine clearance and proteinurea in mycophenolate mofetil (MMF) and azathioprine treatment

Characteristic	MMF (n)	Azathioprine (n)	Total (n)	P value
Improve SrCr	7 (23.3%)	6 (20%)	13 (43.3%)	p=1.000
Improve CrCL	7 (23.3%)	6 (20%)	13 (43.3%)	p=1.000
Improve proteinurea	10 (33.3%)	6 (20%)	16 (53.3%)	p=0.272

P < 0.05 denotes statistical significance

Values are the number of patients (percentage)

SrCr = serum creatinine; CrCl = creatinine clearance

The mean improvement of serum creatinine, creatinine clearance and proteinurea in mycophenolate mofetil and azathioprine treated patients were described in Table 3. The mean improvement of serum creatinine for mycophenolate mofetil group was 11.57±8.44 µmol/L and for the azathioprine group was 6.0±3.79 µmol/L. Therefore, improvement on creatinine clearance for mycophenolate mofetil group was 14.41±10.98ml/min and for the azathioprine group was 9.9±6.5ml/min. As for proteinurea, mycophenolate mofetil group showed mean improvement of 17.23g/L and for azathioprine group was 13.77g/L. Although mycophenolate mofetil treated patients showed higher mean improvement of serum creatinine, creatinine clearance and proteinurea, the result was not statistically significant (p=0.529, p=0.398, p=0.260 respectively).

Table 3: Mean improvement of serum creatinine, creatinine clearance and proteinurea in mycophenolate mofetil (MMF) and azathioprine treated patient

Characteristic	MMF	Azathioprine	P value
Improve SrCr (µmol/L, mean±SD)	11.57±8.44	6.0±3.79	p=0.529
Improve CrCL (ml/min, mean±SD)	14.41±10.98	9.9±6.5	p=0.398
Improve proteinurea(g/L, mean rank)	17.23	13.77	p=0.260

P < 0.05 denotes statistical significance, mean rank for non-parametric test

SrCr = serum creatinine; CrCl = creatinine clearance

DISCUSSION

Mycophenolate mofetil has been used as an immunosuppressive drug in transplantation since long time ago. Over the years, the usage has been investigated further and was used effectively in the treatment of glomerular diseases including lupus nephritis. An older immunosuppressive drug, azathioprine is also extensively used in transplantation and glomerular diseases [12]. Patient with Class III and IV is required an aggressive therapy with glucocorticoids and immunosuppressive therapy due to the proliferative changes of glomeruli (<50% of glomeruli changes in Class III, >50% of glomeruli changes in Class IV) [5-6].

One of the reliable and valid response indices, which are Responder Index for Lupus Erythematosus (RIFLE) can be used to define treatment response in lupus. Complete renal response is defined as proteinurea <0.5gm/24hours, serum creatinine < 1mg/dl (88.4µmol/L), urine RBC count<5/hpf, no RBC cast and normal glomerular filtration rate (GFR) for body mass [13]. In another report by American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria defined the improved response as 25% increase in GFR if baseline estimated GFR is abnormal, at least 50% reduction in urinary protein:urinary:creatinine ratio and change from active urinary sediment (≥5 RBCs/hpf and ≥ 5WBCs/hpf and/or ≥1 cellular cast) to inactive urinary sediment (≥5 RBCs/hpf and ≤5 WBCs/hpf and no cellular cast) [14].

Several clinical trials have demonstrated the effectiveness of mycophenolate mofetil and azathioprine in maintenance treatment of lupus nephritis [9-11]. However, in this study, the effect of both mycophenolate mofetil and azathioprine in improvement of serum creatinine, creatinine clearance and proteinurea were not established. All the treatment groups did not show any significance improvement of mean serum creatinine, creatinine clearance and proteinurea. Nevertheless, the findings may indicate that both mycophenolate mofetil and azathioprine had similar improvement in mean serum creatinine, creatinine clearance and proteinurea in the maintenance treatment of lupus nephritis.

Appropriate treatment is essential to prevent the progression of end-stage renal disease in patient with lupus nephritis [3]. According to the result of this study, there was no significant difference found in the mean improvement of creatinine clearance between mycophenolate mofetil (14.41$\pm$10.98ml/min) and azathioprine (9.9$\pm$6.5ml/min) with p=0.398. This result was consistent with the outcomes Euro-Lupus Nephritis Trial [9]. However, the outcomes of another study showed that mycophenolate mofetil was superior to azathioprine in delaying renal flare (hazard ratio, 0.50; p=0.03) and maintaining renal function (time to end-stage renal disease, 0% in mycophenolate mofetil group and 2.7% in the azathioprine group; p=0.07). The total number of patients in the study was large to make a significant difference result (n=227). The patients were also followed for longer duration (36 months) as compared to our study (12 months) [11].

Incidence of side effects of both mycophenolate mofetil and azathioprine were also determined in this study. Side effects were more common in mycophenolate mofetil group as compared to azathioprine group. Infection was the most reported side effect in this study and the result was consistent from a previous study [11].

The current study findings have highlighted the important outcomes of mycophenolate mofetil and azathioprine in maintenance treatment of lupus nephritis, nonetheless the findings should presume with caution due to several limitations. The limited sample size, limited duration of study and variable medication dose and combination may influence indirectly to the findings. Number of patients who are treated with mycophenolate and azathioprine initially was large. However, several combination therapies with other immunosuppressant medications would limit the patient's selection as this study was done to compare the effectiveness of mycophenolate mofetil and azathioprine as a single agent.

CONCLUSION

Mycophenolate mofetil and azathioprine had similar effectiveness in the maintenance treatment of lupus nephritis. Therefore, both mycophenolate mofetil and azathioprine can be used effectively as initial drug of choice for maintenance treatment in lupus nephritis.

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