Archives of The Medicine and Case Reports
Journal Homepage: https://hmpublisher.com/index.php/AMCR/index
eISSN: 2747-2051

Mycophenolate Mofetil for a Flare Child Lupus Nephritis: A Case Reports

Gina Puspita[1*], Desy Rusmawatiningtyas[2], Sumadiono[3]

[1] Faculty of Medicine, Nursing and Health Science, Universitas Muhammadiyah Yogyakarta, Bantul, Indonesia
[2] Division of Pediatric Intensive Emergency, Department of Pediatrics, Dr. Sardjito General Hospital, Yogyakarta, Indonesia
[3] Division of Allergy and Pediatric Immunology, Department of Pediatrics, Dr. Sardjito General Hospital, Yogyakarta, Indonesia

ARTICLE INFO

Keywords:
Lupus nephritis
Flare
Mycophenolate mofetil
Children
Systemic lupus erythematosus

***Corresponding author:**
Gina Puspita

E-mail address:
gina.puspita@umy.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/AMCR.v2i2.18

ABSTRACT

Renal involvement is the most common complication of systemic lupus erythematosus (SLE) and is also an important predictor of patient mortality. The incidence of flares is estimated at 65% each year in patients with lupus nephritis. Therapy in lupus nephritis with flare also uses high doses of steroid agents and strong immunosuppression agents. Mycophenolate mofetil (MMF) as an immunosuppression agent tends to favor for flare in lupus nephritis. We describe a patient who had a flare in lupus nephritis that resolved with high-dose steroid and MMF. The combination of immunosuppression agents and high-dose corticosteroids is effective for the control of active diseases. Cyclophosphamide as the steroid-sparing agent was discontinued because of adverse effects as well as hematuria. Partial remission was later achieved and maintained with MMF and corticosteroid after five months of protocol treatment. Thus, MMF while maintaining the steroid dose may induce remission for this case.

1. Introduction

SLE in children is more acute and severe than in adult SLE. The study showed that the frequency of kidney, neurological, and hematological involvement in SLE in children was more frequent than in adults.[1] In a study at Sardjito General Hospital in 2007-2012, the initial clinical manifestations that appeared when diagnosed with lupus were nephritis (76.1%), arthritis (67.4%), positive ANA test (63.1%), and mouth ulcer (60.1%).[2]

The goal of successful therapy in lupus nephritis is to achieve complete and persistent remission of renal manifestations without side effects.[3] Close monitoring of disease activity using the SLEDAI score is needed to see the remission response to therapy.2 Several studies reported that the incidence of flares dependent on the therapy. The patients treated with prednisone alone had a probability of renal flare was 75% and for patients treated with prednisone and cyclophosphamide was 30%.[3] Risk factors for flares include decreased doses of steroids or immunosuppression medication, withdrawal of hydroxychloroquine, exposure to sunlight, increased of estrogen hormone, infection, and drugs.[4]

Mycophenolate mofetil (MMF) is an immunosuppression medication known as maintenance therapy since 2006. MMF has a potential action to inhibiting T and B lymphocytes proliferation and autoantibodies production.[5] Previous studies of the MMF used in multitarget with tacrolimus to treat Korean patients with stage III, IV or V and flare who failed to achieve a complete response therapy at 12 months after induction therapy were showed that 53.9% of the patient's response, with 15.4% complete response and 38.5% partial response.[6] Conti (2004) et al, reported that

17.9% of patients with lupus were treated with MMF (mean treatment duration 33.9 ± 31.2 months). Indication therapy for using MMF was lupus nephritis (55.9%) and musculoskeletal manifestation (33%).[7]

2. Case Presentation

A 16-year 7-month-old girl, who had no past medical history, presented with a painless oral ulcer in her mouth and a high fever which started four days prior to regional hospital admission. On another hand, she also complained about a rash on her face, especially after she had outdoor activity. There was no history of taking medicine. She was hospitalized in a regional hospital with diagnosed lupus and got a corticosteroid low dose. For five-month during therapy, she got a flare of high fever and sore throat. She had arthralgia, fatigue, and decreased body weight. She was referred to the primary hospital with a previous suspicion of lupus nephritis because urinalysis showed proteinuria (+3).

At the primary hospital, she had a cough and coryza. Moreover, she also complains of a rash on her face with increasing erythema after sun exposure. On examination, she was sub febrile and follow commands, but more fatigue. Blood pressure was stable at 100/60 mmHg. The head was found with alopecia and malar rash on her face. The mouth found a painless oral ulcer.

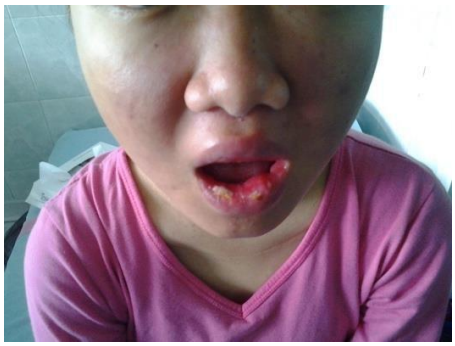
The result of investigations were as follows haemoglobin was 11.3 g/dL (12–16 g/dL), leucocyte count 4710 /uL (4000-10.000/uL), platelet count 93.000 /uL (150.000-440.000/uL). Complement C3 was 23 mg/dL (90-180 mg/dL) and C4 3.4 mg/dL (10- 40 mg/dL). Anti-nuclear antibodies (ANA) was 187.72 IU/mL (10-30 IU/mL) and anti-double stranded deoxyribonucleic acid (antidsDNA) antibody was above 200 IU/mL (<20 IU/mL). Renal function showed creatinine 0.9 mg/dL with glomerular filtration rate was 95 mL/min/1.73 m2. The result of the urinalysis were dipstic proteinuria +3 and hematuria was negative. Analysis for a 24-hour urine collection found the abnormal albumin excretion rate was 35 mg/day (5-10mg/day) and protein/creatinine urine ratio was 1.06 mg/mg (<0.2 mg/mg).

Based on The Systemic Lupus International Collaborating Clinics (SLICC) and American College of Rheumatology (ARA) criteria, the clinical manifestation showed Systemic Lupus Erythematosus with nephritis manifestation with a SLEDAI score was 17. In this case, we didn't perform a biopsy for the workup diagnosis because the parents declined this procedure. Hence, we used the criteria for calcification with lupus nephritis according to the World Health Organization (WHO). The WHO classification assesses the histological pattern and location of the immune complexes. Based on these criteria our patient was classified as lupus nephritis type mesangial class II because we found proteinuria 200-500mg, absent for erythrocyte sediment, serum creatinine was normal, blood pressure was normal, negative or positive dsDNA, and decreased or normal for complement (C3/C4). Therapy given in the induction phase was high doses of corticosteroids 1 mg/kg/day for 8 weeks then gradually tapered off with alternate doses. In the maintenance phase, 500-1000mg/m2 cyclophosphamide was added for 7 times. Adverse event was hematuria after cyclophosphamide in 11th month. The patient had a complete remission after 14 months of the therapy with the result of proteinuria was ± (trace) to 1+ and protein/creatinine urine ratio was 0.21. SLEDAI score was 0.

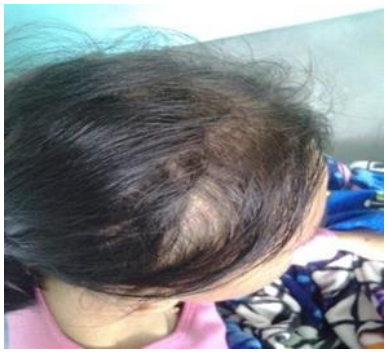
At month 21 of the protocol, the patient had severe flares with an increase in the SLEDAI score 16. The condition at that time was renal impairment in the form of moderate proteinuria flares with increased proteinuria to +3 (300-999 mg/dl) for three consecutive months, followed by hematuria 2+ with 54/uL erythrocyte sediment and 111/uL leukocytes and increased protein/ creatinine ratio to 2.2, arthritis, mucosal disorders in the form of new mucosal ulcers and malar rash. Severe flares are suspected due to recurrent of urinary tract infection and tapering off dose steroid of 0.1mg/kg/day.

The flare of lupus nephritis was treated by dose pulse steroid 10mg/kg/day every three consecutive days for six months and continue with methylprednisolone 1 mg/kg/day orally and gradually reduced. MMF was introduced at 500

mg/m2/12 hours as the steroid-sparing agent. The monitoring results showed that the patient's condition improved with a partial remission marked by a decrease in proteinuria from 3+ (300-999 mg/dl) gradually down to 2+ (100-299 mg/dl), +3 hematuria decreased to negative, decreased erythrocyte sediment from 54 to 37 and leukocyte sediment decreased from 111 to 9, the protein/creatinine ratio decreased from 2.2 at the time of the flare to 1.03 at the 10th month of the protocol. Until this report was written, the patient was still in the stage of partial remission where the decrease in proteinuria reached 1.5 grams/day from baseline and the urinary protein/creatinine ratio ranged from 0.2 to 2. At the end of the observation, the SLEDAI score was also evaluated after changing the protocol, and the result was 0. We repeated anti-dsDNA has been negative and complement C3 and C4 are within normal limits. Her quality of life improves with the improvement of her condition, both physically and mentally. Currently, she has continued her education at Nursing Science college. The patient is also still in routine treatment and follow-up to complete the lupus nephritis protocol.



Oral Ulcer



Alopecia

Figure 1. The first admission to our hospital

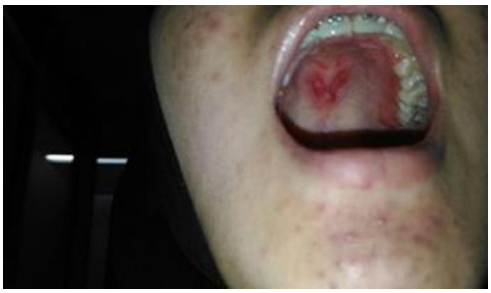


Figure 2. Flare condition (before MMF)

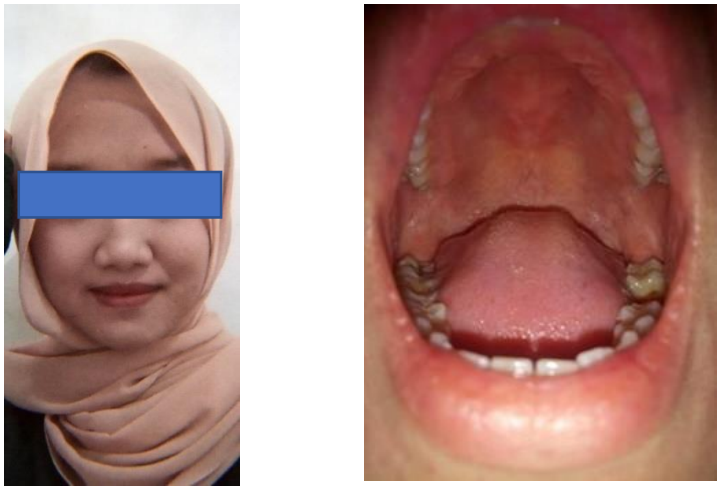


Figure 3. Partial remission after treatment

3. Discussion

The pathophysiology of lupus nephritis occurs due to the accumulation of immune complexes in the glomerular followed by infiltration of T cells and macrophages in the glomerular. Renal involvement is the most common complication of Systemic Lupus Erythematosus (SLE) and is also an important predictor of patient mortality.[8]

The proportion of the incidence of nephritis in adult patients with lupus is around 50-60%, but there is an increased proportion of nephritis incidence in children with lupus by almost 80% in the first 10 years after diagnosis. However, giving aggressive therapy for lupus nephritis will reduce the incidence of kidney failure by 10-30%.[9,10]

Based on the American College of Rheumatology (ACR) criteria, lupus nephritis is a clinical and laboratory manifestation with the following criteria: (persistent proteinuria> 0.5 grams/day or more than +3 by dipstick examination, and/or cellular sediments such as erythrocytes (>5 RBC / field of view), leukocytes (>5 WBC / visual field), hemoglobin, granular, tubular, or mixed) and urinary protein/creatinine ratio >0.5 in the 24-hour measurement.[3] Gold standard for lupus nephritis was renal biopsy for adjusting to protocol therapy. The task force panel had a recommendation for a patient with clinical manifestation of lupus nephritis due to renal biopsy. Hence, these patients include the classification of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) which is divided into six groups.[11]

In this patient, a diagnosis of lupus nephritis was based on several findings. The patient had fulfilled the ACR and SLICC classification criteria for SLE and had an abnormal urinary test like proteinuria, abnormal creatinine/protein ratio, and abnormal albumin excretion rate within 24 hours as determined by nephritis involvement. A renal biopsy didn't perform for this patient because the parents were declined. So, we used WHO criteria for initial therapy.

Therapy for lupus nephritis is divided into two mechanisms initial and maintenance phases. The goal of initial therapy is to complete remission and reduce damage to the nephron. The goal of maintenance therapy is to control diseases activity and decreased to occur of flares. The American College of Rheumatology (ACR) recommended for therapy lupus nephritis consisted of high-dose daily steroid and immunosuppressive medication with cyclophosphamide as most effective for diffuse proliferative glomerulonephritis.[9] Criteria for remission in lupus nephritis were complete remission, partial remission, and no remission. Criteria for complete remission are GFR reaching ≥90 ml/min/1.73m2 or a 25% increase compared to baseline, the urine protein/creatinine ratio <0.2 or negative to trace with a urine dipstick, erythrocyte sediment in urine ≤5 per field of view, and no pathological cylinder is found in the urine. Criteria for partial remission are included complete remission but the urine protein/creatinine ratio range from 0.2 to 2.[12]

A high-dose steroid therapy protocol was given as soon as the child was diagnosed with lupus nephritis as initial therapy. Cyclophosphamide was given as maintenance therapy for this patient. Intravenous cyclophosphamide is given every four weeks for six months with a dose was 1000 mg/m2. The patients had complete remission after 14-month therapy initial and maintenance with a SLEDAI score was 0. Incidence of flare in lupus was 65% every year and for lupus nephritis was 0.[22] flares/patient/year. 13 Frequency of flare common in patients with high serum antibody anti ds DNA. The other risk factor for flare in lupus was decreased steroid dose or immunosuppression medication, withdrawal of hydroxychloroquine, sun exposure, increase of estrogen hormone, infection, and drug exposure.4 Therapy for flare in lupus nephritis used three immunosuppressive medications such as cyclophosphamide, MMF, and azathioprine (AZA). Previous studies reported that MMF had superior to other drugs with fewer adverse effects. Henderson et al., (2012), reported that MMF is as effective as intravenous cyclophosphamide in achieving stable kidney function (RR:1.05, 95% CI 0.94 to 1.18) and complete remission of proteinuria (RR: 1.16, 95% CI 0.85 to 1.58). The study of RCT about safety between MMF versus Cyclophosphamide showed that leukopenia was less common in MMF (RR: 0.65, 95% CI 0.44 to 0.96), reduction of ovarian failure (RR: 0.15, 95% CI 0.03 to 0.80), and less alopecia (RR: 0.22, 95% CI 0.06 to 0.86) compared to cyclophosphamide.14 MMF is more effective than AZA for preventing renal relapse (RR: 1.83, 95% CI 1.24 to 2.71). The adverse event didn't differ between MMF and AZA except for cytopenia which is more frequent in AZA than in MMF (p=0.03).[14, 15]

MMF is an immunosuppression medication which more lymphocyte-selective than other purine antagonists like AZA. Moreover, MMF had an inhibitory effect on the maturation of human dendritic cells which important role in the pathogenesis of lupus. Dendritic cells had a function for producing type 1 interferon, presenting antigens to the T lymphocytes and leading to their differentiation, proliferation, and activation.

Another function of MMF was to inhibit smooth muscle proliferation and reduce high-density lipoprotein oxidation which play role in the progression of atherosclerosis.[5]

We decided to give MMF to this patient's flare because of the evidence to suggest that MMF works well in lupus nephritis and less the adverse event. Furthermore, the patient's had an adverse effect with cyclophosphamide. We didn't find severe adverse events since MMF therapy for this patient. After five months of routine consumption of MMF and pulse dose of corticosteroid, the patient improved to partial remission.

Several studies reported that complete remissions are significantly longer than partial remissions. The meantime of complete remission was 16 months with a mean value of 10.5 months compared to the mean partial remission of 5.8 months. 16 Patients who never had a flare had the significantly better stable condition and more complete remission than patients who had experienced a flare. 13 Thus, assessment of disease activity during follow-up of patients with lupus nephritis would influence the long-term outcome in these patients.

4. Conclusion

Mycophenolate mofetil was a good medication choice as an immunosuppression agent. Recent studies showed that MMF can introduce in initial and maintenance therapy. The result of therapy is generally well tolerated and less toxic than AZA and cyclophosphamide. MMF can be considered a therapeutic option for flare in lupus nephritis because the outcome is good.

5. References

1. Mina R. Response to Therapy, Damage Accrual Compared to Adult. Rheum Dis Clin North Am. 2010; 36(1): 53–80.
2. Farkhati MY, Hapsara S, Satria CD. Antibodi Anti DS-DNA Sebagai Faktor Prognosis Mortalitas pada Lupus Eritematosus Sistemik. Sari Pediatr. 2012; 14(2): 2–8.
3. Ponticelli C, Moroni G. Flares in lupus nephritis: Incidence, impact on renal survival

and management. Lupus. 1998; 7(9): 635–8.
4. Fernandez D, Kirou KA. What causes lupus flares? Curr Rheumatol Rep. 2016; 18(3): 1–10.
5. Mok CC. Mycophenolate mofetil for lupus nephritis: An update. Expert Rev Clin Immunol. 2015; 11(12): 1353–64.
6. Choi CB, Won S, Bae SC. Outcomes of multitarget therapy using mycophenolate mofetil and tacrolimus for refractory or relapsing lupus nephritis. Lupus. 2018; 27(6): 1007–11.
7. Conti F, Ceccarelli F, Perricone C, Massaro L, Cipriano E, Pacucci VA, et al. Mycophenolate mofetil in systemic lupus erythematosus: results from a retrospective study in a large monocentric cohort and review of the literature. Immunol Res. 2014; 60(2–3): 270–6.
8. Lech M, Anders H-J. The Pathogenesis of Lupus Nephritis. J Am Soc Nephrol [Internet]. 2013; 24(9): 1357–66.Available from:http://www.jasn.org/cgi/doi/10.1681/ASN.2 013010026
9. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012; 64(6): 797–808.
10. Costenbader KH, Desai A, Alarcon G, Hiraki LT, Shaykevich T, et al. Trends in the Incidence, Demographics and Outcomes of End-Stage Renal Disease Due to Lupus Nephritis in the U.S.,1995-2006. Arthritis Rheumatol. 2011; 63(6): 1681–8.
11. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: Results from an international inception cohort study. Rheumatol (United Kingdom). 2015;55(2):252– 62.
12. Chen YE, Korbert SM, Katz RS, Schwartz MM, Lewis EJ, Roberts JL, et al. Value of complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008; 3(1): 46–53.
13. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. Nephritic flares are predictors of bad long-term renal outcome in lupus nephritis. Kidney Int. 1996; 50(6): 2047–53.
14. Henderson L, Masson P, Jc C, Rs F, Ma R, et al. Treatment for lupus nephritis (Review). Cochrane Database Syst Rev Art. 2012; (12): 1–127.
15. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: Results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69(12):2083–9.
16. Fernandes das Neves M, Irlapati RVP, Isenberg D. Assessment of long-term remission in lupus nephritis patients: A retrospective analysis over 30 years. Rheumatol (United Kingdom). 2015; 54(8): 1403–7.