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ORIGINAL ARTICLE

Cyclophosphamide and Mycophenolate Mofetil as Induction Therapy in Lupus Nephritis

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Abstract

Background/Aim: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystemic involvement. Almost 50 % of patients who suffer from systemic lupus erythematosus have lupus nephritis (LN) as well. Mycophenolate mofetil (MMF) or intravenous cyclophosphamide (CYC) are recommended as preferred therapy. The aim of this study was to see how MMF and CYC, when compared, are efficient in dealing with LN.
Methods: Study included 53 SLE patients with biopsy-proven class III and class IV LN. Twenty-two patients (42 %) were treated with MMF (dosage 2-3 g/day) and 31 patients (58 %) were treated with CYC (0.5 to 1.0 g/m^2 in monthly pulses) in a 24-week induction study. Outcome of interest was the improvement in serum creatinine, proteinuria and creatinine clearance. Primary end point included complete renal remission defined as serum creatinine within 25 % of baseline before flare and proteinuria < 0.5 g/24 h. Secondary end point included complete renal remission in follow-up period.
Results: The results revealed that response between two groups was not notably different (X^2 = 0.151, p = 0.697). Four out of 22 patients (18.2 %) in MMF group and 7 out of 31 patients (22.6 %) in CYC group had complete renal remission. Most patients from both groups showed improvement from the clinical point of view. Secondary end point was also similar between treatment groups.
Conclusion: The study showed same efficiency between these treatment groups, MMF and CYC as induction for LN. No crucial differences were identified between MMF and CYC groups in terms of renal remission.

Key words: Lupus erythematosus, systemic; Lupus nephritis; Cyclophosphamide; Mycophenolic acid; Mycophenolate mofetil.

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Introduction

Systemic lupus erythematosus (SLE) is a condition that has an unpredictable course with alternating exacerbations and remissions and with a high risk of affecting all organ systems.[1] To set the diagnosis one needs to take into account the clinical characteristics and the presence of appropriate autoantibodies. The kidney is an organ which is the most often afflicted by this condition in the form of lupus nephritis (LN), which occurs in about half of SLE patients.[2, 3] The most important immune complex in immune-pathogenesis is anti-double-stranded DNA (anti-dsDNA) bound to DNA. This complex is deposited in the basement membrane of the glomerulus, more precisely in

the mesangial, subepithelial and subendothelial spaces. This leads to an inflammatory cascade with complement activation, which causes the migration of neutrophils and other cells of the immune system to the aforementioned part of the kidney.[4-6]

Since timely detection and treatment of kidney damage can significantly affect the disease outcome, it is of importance to do the assessment of kidney functioning in SLE patients. LN is present in most SLE patients, even in those patients who do not show signs of the kidney disorder from the clinical point of view. The LN is monitored by measuring: creatinine, the ratio of albumin to creatinine in the urine and the analysis of the urine sample itself. This helps detect the increase of creatinine in serum from the initial value, in addition to the presence of proteinuria, which is often seen in LN patients. Given that LN has a high morbidity, timely course of medication is one of the most important components in stopping advancement to end-stage renal disease.[7-10]

The course of LN treatment is determined by how acute the disease is and how high the risk of progressive kidney damage is. Aside from antimalarial drugs and renin-angiotensin-aldosterone system (RAAS) inhibitors, in order to decrease inflammation and to have autoimmunity suppressed, immunosuppressants and large doses of glucocorticoids are used for proliferative LN (class III, IV or III/IV+V) and class V of LN with nephrotic syndrome. This starting treatment phase, which is usually 3 to 6 months long, is known as the induction phase.[2]

In LN active phase, it is recommended to use glucocorticoids with mycophenolate mofetil (MMF) or cyclophosphamide (CYC) as basic medicine.[11] In 2019 updated EULAR/ ERA-EDTA recommendations for LN,[12] the goal was to reduce proteinuria by more than 25 % with a stabile glomerular filtration rate (GFR; ± 10 % of baseline) the first 3 months after the start of treatment, to reduce proteinuria by ≥ 50 % after 6 months and < 0.5–0.7 g/24 h proteinuria at 12–24 month mark.[13]

With active proliferative LN, the intravenous CYC (500 mg every 15 days, during three months) or MMF (2–3 g/day), both in combination with glucocorticoids (recommended intravenous administration of methylprednisolone, followed by oral prednisolone 0.3–0.5 mg/kg/day) are used during induction treatment. The use of MMF together with CNI or big-dose CYC are other types of treatment for those with nephrotic-grade proteinuria and unfavourable prognosis. MMF or azathioprine should be used in the follow-up long-term treatment. More attention has been given to the necessity to minimise patient exposure to glucocorticoids.

The aim of this study was to see how MMF and CYC, when compared, are efficient in dealing with LN.

Methods

This study was carried out at the Clinic for Internal Disease, Department of Rheumatology, Banja Luka, Bosnia and Herzegovina. The study was retrospective and included 53 patients of both sexes diagnosed with SLE who had class III and class IV LN confirmed by biopsy.

The criteria used for inclusion in the study were as follow: patients 18 and older, biopsy-proven class III and class IV LN with nephrotic-grade proteinuria (defined by the presence of > 3 g of protein in the urine during a 24 h collection) and a signed letter of approval to take part in the study. The patients who were not included in the study are those who had another autoimmune disease, kidney disease, myocardial infarction, stroke, cancer, previously underwent MMF therapy, intravenous CYC therapy in the previous year, monoclonal antibody therapy in the last month and were pregnant or lactating. The study did not cover the biopsy-proven class I, II, V and VI cases.

The exposure of interest was induction immunosuppressive therapy received within the first 24 weeks of biopsy. The main validation measure was a complete renal remission defined as creatinine in serum within 25 % of baseline value before nephritis and proteinuria < 0.5 g/24 h. A secondary endpoint included complete renal remission at five-year follow-up period.

There were two patient groups: Group I: 22 patients with LN treated with MMF for 24 weeks, dose 2-3 g/day; Group II: 31 patients with LN treated with intravenous CYC (0.5 to 1.0 g/m^2 in monthly pulses) for 24 weeks. Both groups were given intravenous methylprednisolone too

(initially 500 mg for three days), followed by oral prednisone 0.5-0.3 mg/kg/day.

The laboratory tests were performed before and during treatment every month. The Central Laboratory of the Clinical Centre collected samples for biochemical analyses. Serum creatinine (sCr), creatinine clearance (measured from 24-h-urine sample), urinary creatinine (uCr) and protein values in 24-h-urine were analysed. The samples of venous blood necessary for biochemical analyses were taken in the morning after fasting.

Two types of comparison were performed to test the mean values of individual study variables: within each group (sample) and between groups. The study variables were presented using measures of descriptive statistics. The Pearson Chi-square test was used to assess the complete renal remission between the two groups, as well as to compare renal remission during the follow-up period.

Results

Fifty-three patients were included in the study. The age of the patients ranged from 25 to 74 (mean: 59.69 years, SD 13.2). There were 43 (81 %) female respondents and 10 (19 %) male respondents. Thirty-seven patients (71 %) had completed high school, 37 (23 %) primary school and 3 (6 %) vocational education. A large number of patients was from urban areas, 88 % of them and 12 % from rural areas. Both treatment groups had a similar number of patients who underwent therapy.

Four of 22 patients in the MMF group and 7 of 31 patients in the CYC group had complete renal remission. Thus, the primary efficacy endpoint was achieved by 4 (18.2 %) of 22 patients in the MMF group compared with 7 (22.6 %) of 31 patients in the CYC group. It has not been identified a notable distinction from the statistical point of view (χ^2 = 0.151, p = 0.697) in the response rate between the two groups (Figure 1).

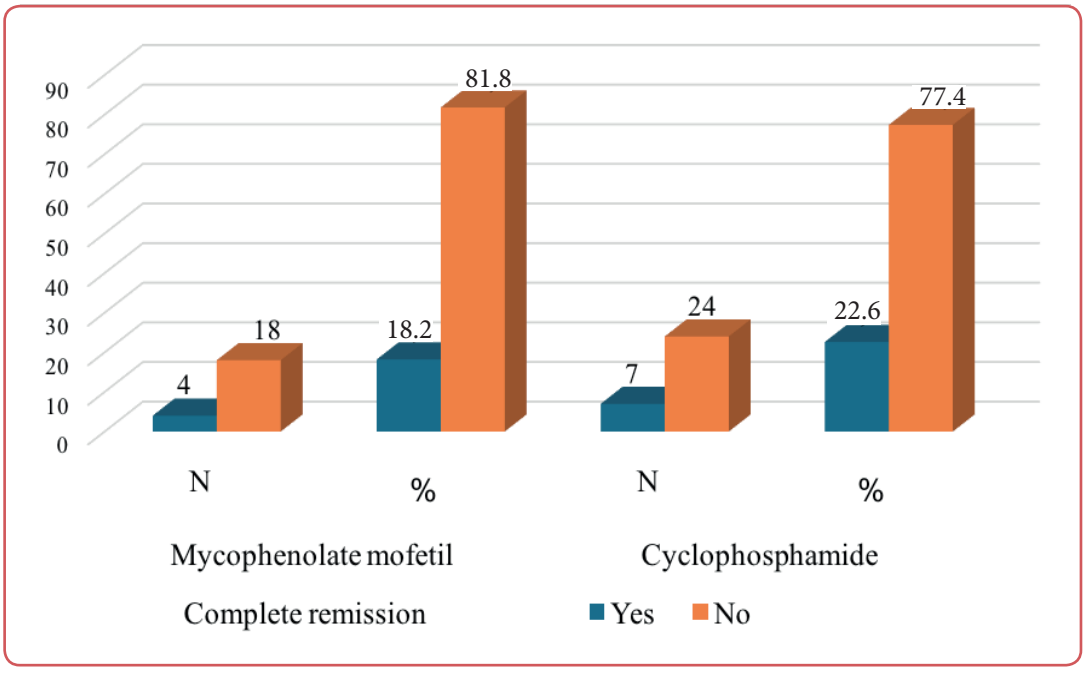

Figure 1: Patients with complete renal remission after six months of treatment with mycophenolate mofetil and cyclophosphamide

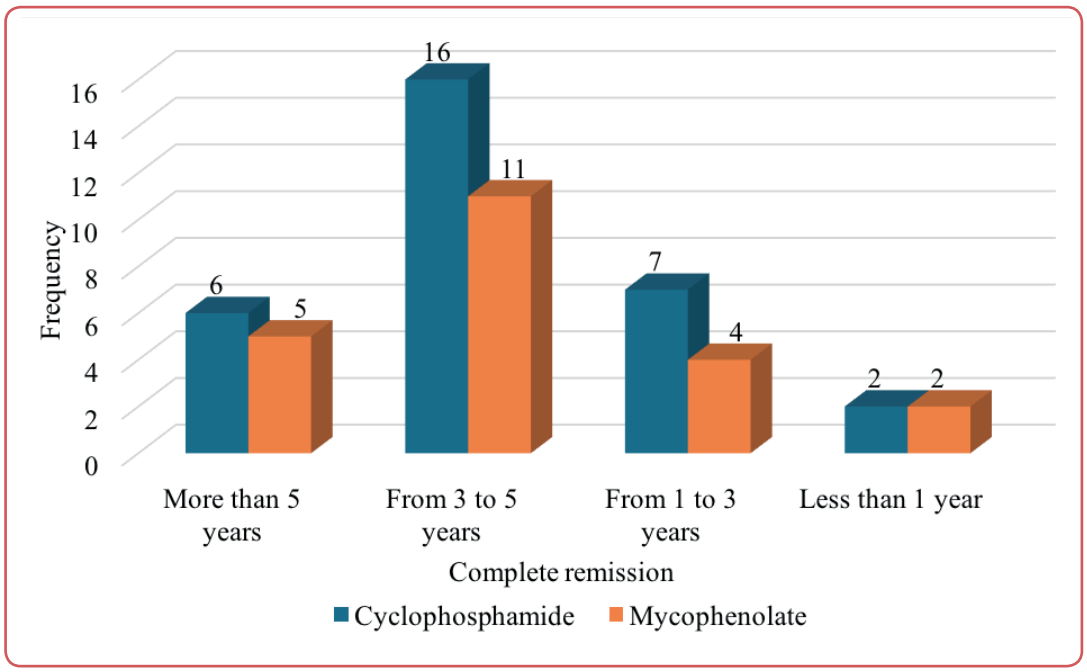

Figure 2: Complete renal remission in five years follow-up

It has not been identified a notable distinction from the statistical point of view in complete renal remission during the following 5-year period between study groups when the study was completed (χ^2 = 0.316, p = 0.957). It showed a sustained steady kidney remission in the first two groups (Figure 2).

Discussion

CYC (oral or intravenous), as a gold standard in the LN treatment, has been used since the 1980s after the publication of a National Institutes of Health (NIH) study. This study showed that adding intravenous CYC during treatment with glucocorticoids significantly improved LN outcomes and reduced the risk of renal failure compared to the treatment with glucocorticoids alone. The 370 patients were included in the Aspreva Lupus Management Study. This study made a comparison between MMF (3 g/day) and CYC treatment for LN and showed the same effectiveness at 6-month and at 3.5-year check. The remission rates presented in this study were 56 % in the MMF group and 53 % in the CYC group after 6-month treatment period and 62 % for the MMF group and 59 % for the CYC group after 3.5-year treatment period. Taking into account all studies, the proliferative LN can be successfully treated with both small doses of CYC and MMF as induction therapy alternatives.[2] MMF was as effective as CYC in induction treatment in studies in Hong Kong,[14, 15] Malaysia,[16] China[17] and the United States.[18]

Presented study provides a comparison of how effective both MMF and CYC are in treating LN. It was found that MMF has a similar remission rate to CYC, so results do not deviate from those of other studies. The small sample size is a limitation of this study. In addition, it is important to take into consideration the cost-benefit relation. Even though MMF costs more than intravenous CYC, there are some costs related to CYC infusion, including infusion and antiemetic costs.

Conclusion

LN can be effectively treated with both MMF and CYC. It was not identified a notable distinction between the MMF and IVC groups in terms of renal remission at 5-year follow-up.

Ethics

The study protocol was approved by the University Clinical Centre of the Republic of Srpska, decision No 01-3-58, dated 5 May 2016. The patients were asked to sign an informed letter of approval before they took part in the study and for publishing anonymised data. This study was carried out in concurrence with The Declaration of Helsinki, 8th Revision, 2013.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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