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Outcome of Leflunomide in the Treatment of Proliferative Lupus Nephritis Compared to Cyclophosphamide

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Abstract

Background: Lupus nephritis (LN) is one of the most common presentations of Systemic lupus erythematosus (SLE). Cyclophosphamide is one of the key immunosuppressive agents for the management of LN. Leflunomide is an isoxazole immunomodulatory agent has been shown to be safe, well tolerated and effective in SLE and LN. **Objective:** To evaluate the outcome of leflunomide in the treatment of proliferative lupus nephritis compared to cyclophosphamide. **Method:** This randomized clinical trial was held in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2017 to August 2019. A total of 66 patients of proliferative lupus nephritis who need induction therapy were enrolled in this study. Leflunomide 100 mg/day for consecutive 3 days followed by 0.5 mg/kg/day in divided dose was given in experimental group (n = 32) and intravenous cyclophosphamide 0.5 gm/m^2 of body surface area monthly pulse was given in control group (n = 34). All study patients have received prednisolone and hydroxychloroquine according to KDIGO guideline then followed up monthly for 6 months. Outcomes were measured at 6th month by renal function [S. Creatinine, 24 hours urinary total protein (24-hr UTP)], changes in SELENA-SLEDAI

score, anti-ds DNA level, serum complement levels (serum C3 & C4), remission (complete/partial) and adverse drug responses. **Result:** In experimental group, remission occurred in 18 (56.3%) patients and no remission in 14 (43.7%) patients. In control group, remission occurred in 24 (70.6%) patients and no remission in 10 (29.4%) patients. Adverse effects in experimental group were: elevated ALT (6.3%), hypertension (12.5%), infection (6.3%) and amenorrhea (12.5%). In control group, adverse effects were mainly leucopenia (5.9%), infection (17.7%) and amenorrhea (29.4%). Intergroup analysis for treatment responses and adverse effects showed no significant difference ($p > 0.05$). **Conclusion:** Leflunomide combined with prednisolone is effective in the induction treatment of proliferative lupus nephritis in Bangladeshi patients in terms of response rate and adverse effects.

Keywords

Cyclophosphamide, Leflunomide, Lupus Nephritis (LN), Systemic Lupus Erythematosus (SLE)

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that has potential to affect every organ in the body most commonly; the skin, kidneys, brain and joints. Kidney involvement, that is, lupus nephritis (LN), accounts for the most morbidity and mortality in SLE [1]. LN is an immune complex glomerulonephritis that is a common feature of SLE. Multiple mechanisms may contribute to the pathophysiology of LN; including glomerular deposition of auto-antibodies, complement activation, cellular proliferation, release of chemokines and pro-inflammatory cytokines leading to inflammation and fibrosis [2].

In LN all four renal compartments namely-glomeruli, tubules, interstitium, and blood vessels may be affected. Renal involvement in SLE is extremely diverse, ranging from asymptomatic urinary findings to fulminant renal failure or florid nephrotic syndrome [3] [4].

The reported incidence of clinically important kidney disease in systemic lupus is about 38% with more than half developing nephritis during the first 10 years of disease [5]. Of those who develop clinical LN, 40% - 60% have overt kidney disease at the time lupus is diagnosed. The prevalence of lupus nephritis (LN) is significantly higher in Asian, African American and Hispanic populations [6]. The peak incidence of lupus is 15 - 45 years of age, with women outnumbering men by 10:1 [7].

LN is a relapsing condition and relapses are associated with development of chronic kidney disease (CKD). It was observed that end-stage renal disease (ESRD) developed around 8% to 15% of patients with LN [7]. Forty percent of complete responders experienced a kidney relapse within a median of 41 months after remission, and 63% of partial responders had a kidney flare within a me-

dian of 11.5 months after response [8].

Between 20% and 70% of patients with LN are reported to be resistant to immunosuppressive therapy, with higher failure rates reported in studies with shorter follow-up periods [9]. Cyclophosphamide is one of the key immunosuppressive agents for the management of LN [10]. Several studies were performed to find out the efficacy and safety of cyclophosphamide in lupus nephritis patients. Of those, Illei *et al.* found complete remission was 50.34% and partial remission was 13.1% in cyclophosphamide treated lupus patients [8]; while Moroni et al. found it in 63.4% and 19.3% patients respectively [11]. Annavarajula *et al.* showed complete remission rate was 51.28% and partial remission rate was 30.77% [12]. Recently it was reported that complete, partial and no remission rates were 53%, 19% and 21.4% in cyclophosphamide treated lupus patients respectively [13]. Regarding side effects of cyclophosphamide; Sahay *et al.* found amenorrhea in 21.4%, infections in 17.8%, leucopenia in 3.5%, diarrhea in 19.6% and alopecia in 25% patients [13]. Similarly, Yee *et al.* found amenorrhea, infection and leucopenia in 7.7%, 38.5% and 7.7% of cyclophosphamide treated lupus patients respectively [14]. Hu *et al.* in their study for patients with diffuse proliferative lupus nephritis with mycophenolate mofetil versus cyclophosphamide therapy found gastrointestinal symptoms was 43.5% and infection was 30.4% [15]. Li *et al.* performed similar type of study where side effects were mainly infection, leucopenia and irregular menstruation; these were 40%, 05% and 20% respectively [16]. Therefore, efforts have been made to explore more effective therapeutic methods with favorable safety profile.

Leflunomide is an isoxazole immunomodulatory agent. It was introduced in 1998 for the treatment of rheumatoid arthritis and has been found to be as effective as methotrexate and sulfasalazine [17]. Since it was approved by the United States Food and Drug Administration [USFDA] to be used in rheumatoid arthritis, leflunomide has been increasingly used in clinical applications [18]. As an immunosuppressive regimen, leflunomide has an inhibition effect on proliferation and activity of B and T cell, making it a reasonable candidate for treatment of LN [19]. Many experimental models and few clinical studies have shown that leflunomide is safe, well tolerated and effective in LN. Among those, Zhang *et al.* observed 23% of patients in the leflunomide group and 27% of patients in the cyclophosphamide group achieved complete remission, while 56% of patients in the leflunomide group and 42% of patients in the cyclophosphamide group achieved partial remission [19]. In another study; Xia *et al.* found complete and partial remission was 61% and 28.5% respectively in LN patients treated with leflunomide [20]. So on an average, almost fifty percent proliferative lupus nephritis patients achieved remission with leflunomide. Regarding adverse effects; Cao *et al.* found side effects in leflunomide treated lupus patients were mainly alanine transaminase (ALT) abnormality, gastrointestinal symptoms, rash, alopecia, leucopenia and infection; those percentages were 7.1, 9.6, 5.1, 3.6, 0.74 and 9 respectively [21]. It was reported that leflunomide can be used safely

in women of reproductive age without risk of infertility and can also be used in resistant LN cases [22]. But there are scarce evidences on efficacy and safety of leflunomide in patients with LN among Bangladeshi adults. Therefore, this study intended to evaluate the outcome of leflunomide in the treatment of lupus nephritis compared to cyclophosphamide.

2. Methodology

This randomized clinical trial was conducted in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2017 to August 2019 among sixty six (66) patients, who were diagnosed as lupus nephritis (class III/IV). The study was approved by the Ethical Review Committee, BSMMU, Dhaka, Bangladesh.

Adult SLE patients of both sexes, diagnosed as LN, admitted in the Department of Nephrology, BSMMU were evaluated for eligibility for this study. Out of those patients who were class III/IV LN diagnosed histologically (urinary active sediment with UTP < 3.5 gm/day) or clinically (urinary active sediment with UTP ≥ 3.5 gm/day) and willing to participate in this study were enrolled. Pregnant women and lactating mother, patient with hypertension (Blood pressure > 140/90 mmHg), diabetic patient, serum creatinine > 2 mg/dl or dialysis dependent patients or kidney transplant recipient, patient hypersensitive to cyclophosphamide or leflunomide, patient with active infection, patient with active malignancy or altered liver function (serum ALT > 2 times of upper limit of normal value) were excluded from the study. All information was explained to each study patient about the natural history and pathophysiology of SLE, current treatment options and outcome of class III/IV LN. Then the subjects were thoroughly appraised about the study as well as drug information which includes efficacy and safety of cyclophosphamide and leflunomide. Prior to the enrollment in this study informed written consent was obtained from each study patient.

2.1. Sample Size Estimation

For the purpose of simplicity, we assumed that the groups were of same size

Formula:

$$N_1 = \frac{\{p_1(100-p_1)+p_2(100-p_2)\}(z_\alpha + z_\beta)^2}{(p_1-p_2)^2}$$

Here,

N_1 = desired sample size in each group.

p_1 = experimental group response = 62% [18] [20].

p_2 = control group response = 33% [18] [20].

z_α = z-value of standard normal distribution at 5% level of significance = 1.96.

z_β = z-value of standard normal distribution at 80% power = 0.84.

So,

$$N_1 = \frac{\{62(100-62)+33(100-33)\}(1.96+0.84)^2}{(62-33)^2}$$
$$= \frac{\{2356+2211\}(1.96+0.84)^2}{(62-33)^2}$$
$$= \frac{4567(1.96+0.84)^2}{841}$$
$$= \frac{35805}{841}$$
$$= 42.57$$
$$= 43$$

Considering 10% drop out $= \frac{N_1}{1-10} = \frac{43}{1-10} = 4.7 = 5$.

The sample for each group = 43 + 5 = 48.

According to this formula, sample size was 48 for each study group that was total 96 in both groups. Because it was a single centre study and time constraints, a total of 66 patients were taken conveniently for this study. They were randomly assigned into two groups with the help of a computerized research randomizer website, where every patient had equal chance to be assigned into any one of the groups (experimental group or control group).

Experimental group: This group consisted of 32 patients who received tablet leflunomide 100 mg/day for consecutive 3 days followed by 0.5 mg/kg/day for 6 months [6].

Control group: This group consisted of 34 patients who received injection cyclophosphamide 0.5 gm/m^2 body surface area monthly for 6 months [6].

All patients received intravenous methyl-prednisolone 1 gm daily for consecutive 3 days followed by oral prednisolone, intial dose of 1 mg/kg/day for around 6 weeks and then tapered according to clinical response. They also received oral hydroxychloroquine 6 mg/kg/day and concomitant other medications as needed according to KDIGO guideline [6]. Patients in both groups were followed up monthly for 6 months. They were gone through baseline investigations before treatment and then investigate monthly for 6 months.

The renal histology was classified according to the International Society of Nephrology/Renal Pathology Society. According to the abbreviated version of the classification, combined classes III/V or IV/V were considered as class III or IV, respectively [23]. Out of those patients who were class III and IV LN diagnosed histologically without any features of exclusion criteria and willing to participate in this study were finally enrolled for this study. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) – Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)/SELENA-SLEDAI score was used to assess kidney disease activity in each patient before and six months after treatment [24].

Before starting the treatment baseline levels of complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine routine microscopic examination (urine-R/M/E), 24-hour urinary total protein (24-hr UTP), serum creatinine, estimated glomerular filtration rate (e-GFR), serum alanine transaminase (ALT), antinuclear antibody (ANA), serum anti-ds DNA antibody (Anti-ds DNA) and serum levels of complement components (C3/C4) were measured in each study participant. After six months of treatment; CBC, ESR, CRP, Urine R/M/E, 24-hr UTP, S. creatinine, e-GFR, ALT, ANA, Anti-ds DNA and serum complement levels (C3/C4) were again measured.

2.2. Kidney Disease Improving Global Outcome (KDIGO 2012) Definition of Remission to Treatment for Lupus Nephritis [6]

Complete remission: Return of serum creatinine to previous baseline, plus a decline in the urinary protein creatinine ratio (uPCR) to <500 mg/g (<50 mg/mmol).

Partial remission: Stabilization (±25%), or improvement of serum creatinine, but not to normal, plus a >50% decrease in uPCR. If there was nephrotic-range proteinuria (uPCR >3000 mg/g [>300 mg/mmol]), improvement requires a > 50% reduction in uPCR, and a uPCR <3000 mg/g [<300 mg/mmol].

No remission: Not achieving either partial or complete remission after six months of treatment.

2.3. Statistical Analysis

Statistical analysis was performed by using windows based computer software with Statistical Packages for Social Sciences (SPSS) version-22. Quantitative data were expressed as mean and standard deviation (SD); qualitative data were expressed as frequency and percentage. Level of significance was examined by paired "t"-test, unpaired "t"-test, Chi-square test and Fisher's exact test. A p-value ≤ 0.05 was considered statistically significant.

3. Results and Observations

A total of 66 LN patients were evaluated over a period of July 2017 to August 2019. Mean age of the study patients was 28.88 ± 8.26 years in experimental group and 31.12 ± 11.12 years in control group. Females were predominant to males in both groups (30:2 and 32:2). Distribution of subjects on the basis of age, gender, serum creatinine, estimated glomerular filtration rate (e-GFR), ALT, 24-hr UTP, Anti-ds-DNA, serum complements (C3/C4), SELENA-SLEDAI score and renal histology did not show any statistically significant difference ($p > 0.05$) (Table 1).

After 6 months of treatment, it was found that; 24-hr UTP, Anti-ds DNA and SELENA-SLEDAI scores were significantly decreased and serum complement levels (C3/C4) were significantly increased from baseline in both groups ($p < 0.05$). Regarding serum creatinine, although mean baseline and 6 months after

Table 1. Baseline characteristics of the study subjects in two group (N = 66).

	Experimental group (n = 32)	Control group (n = 34)	p-value
Age (years)	28.88 ± 8.26	31.12 ± 11.12	0.518[a]
Gender (female/male)	30/2	32/2	1.000[b]
Serum creatinine (mg/dl)	1.05 ± 0.32	0.96 ± 0.34	0.472[a]
eGFR (ml/min/1.73m^2)	84.19 ± 27.79	76.85 ± 34.90	0.510[a]
ALT (g/L)	42.4 ± 2.13	41.4 ± 2.37	0.081[a]
24-hr UTP (gm/day)	3.98 ± 1.88	3.82 ± 2.27	0.833[a]
Anti-ds DNA (U/ml)	116.78 ± 68.83	125.19 ± 68.00	0.726[a]
Serum C3 (g/L)	0.47 ± 0.20	0.49 ± 0.33	0.796[a]
Serum C4 (g/L)	0.14 ± 0.20	0.09 ± 0.07	0.336[a]
SELENA-SLEDAI score	18.13 ± 4.92	20.0 ± 3.46	0.213[a]
Renal histology			
Class III	17 (53.1%)	14 (41.2%)	0.331[b]
Class IV	15 (46.9%)	20 (58.8%)	

Data were expressed as frequency or mean ± SD. [a]Unpaired t test and [b]Chi-square test were done to measure the level of significance.

treatment values were within normal limit in both groups but it was significantly decreased in experimental group (p = 0.044). Intergroup analysis in values of 24-hr UTP, serum creatinine, Anti-ds DNA, serum complement levels (C3/C4) and SELENA-SLEDAI scores showed no significant difference (p > 0.05) (**Table 2**).

After 6 months of treatment, 8 (25.0%) patients in experimental group and 10 (29.4%) patients in control group achieved complete remission. Regarding partial remission, it was 10 (31.3%) patients in experimental group and 14 (41.2%) patients in control group. There was no remission observed among 14 (43.7%) patients in experimental group and 10 (29.4%) patients in control group. The remission (complete remission/partial remission) rates were relatively higher in control group, but that was not statistically significant (p = 0.688) (**Table 3**).

Major adverse events observed in the experimental group were; elevated ALT in 2 (6.3%) patients, hypertension in 4 (12.5%) patients, infection in 2 (6.3%) patients and amenorrhea in 4 (12.5%) patients. While in control group; leucopenia was in 2 (5.9%) patients, infection in 6 (17.7%) patients and amenorrhea was observed in 10 (29.4%) patients. Comparatively higher number of patients in control group were developed adverse effects [18 (52.9%) in control group and 12 (37.5%) in experimental group], but there was no significant difference between the groups (p = 0.373) (**Table 4**).

Table 2. Comparison of outcome variables before and after treatment between two groups (n = 66).

	Experimental group (n = 32)	Control group (n = 34)	p-value
24-hr UTP (gm/day)			
At baseline	3.98 ± 1.88	3.82 ± 2.27	0.833
After 6 months	0.66 ± 0.37	1.14 ± 1.08	0.220
p-value	**0.002**	**<0.001**	
Serum creatinine (mg/dl)			
At baseline	1.05 ± 0.32	0.96 ± 0.34	0.472
After 6 months	0.85 ± 0.20	1.02 ± 0.23	0.142
p-value	**0.044**	0.993	
Anti-ds DNA (U/ml)			
At baseline	116.78 ± 68.83	125.19 ± 68.00	0.726
After 6 months	21.37 ± 9.07	21.24 ± 19.83	0.986
p-value	**0.009**	**<0.001**	
C3 (g/L)			
At baseline	0.47 ± 0.20	0.49 ± 0.33	0.796
After 6 months	1.03 ± 0.32	1.02 ± 0.28	0.964
p-value	**<0.001**	**<0.001**	
C4 (g/L)			
At baseline	0.14 ± 0.20	0.09 ± 0.07	0.152
After 6 months	0.22 ± 0.13	0.23 ± 0.09	0.622
p-value	**0.001**	**<0.001**	
SELENA-SLEDAI score			
At baseline	18.13 ± 4.92	20.0 ± 3.46	0.213
After 6 months	4.89 ± 2.85	6.23 ± 4.27	0.401
p-value	**<0.001**	**<0.001**	

Unpaired "t" test was done between groups and paired "t" test was done within groups.

Table 3. Comparison of remission between two groups (N = 66).

Outcome	Experimental group (n = 32) n (%)	Control group (n = 34) n (%)	p-value
Complete remission	8 (25.0%)	10 (29.4%)	
Partial remission	10 (31.3%)	14 (41.2%)	0.473
No remission	14 (43.7%)	10 (29.4%)	

Chi-square test was done to measure the level of significance.

Table 4. Adverse effects of the study subjects (N = 66).

Adverse effect	Experimental group (n = 32) n (%)	Control group (n = 34) n (%)	p-value
Elevated ALT	2 (6.3)	0 (0.0)	0.446
Hypertension (HTN)	4 (12.5)	0 (0.0)	0.107
Leucopenia	0 (0.0)	2 (5.9)	0.499
Infection	2 (6.3)	6 (17.7)	0.298
Amenorrhea	4 (12.5)	10 (29.4)	0.168
Total	12 (37.5)	18 (52.9)	0.312

Fisher's Exact test was done to measure the level of significance.

4. Discussion

Systemic lupus erythematosus (SLE) is a relapsing autoimmune disease caused by loss of tolerance to self-antigens, the production of auto-antibodies and deposition of complement-fixing immune complexes (ICs) in injured tissues [25]. Lupus nephritis is (LN) an immune-mediated glomerulonephritis and one of the most serious consequences in patients with SLE.

Since SLE requires long-time treatment therapy, so it is very important to define medicines that are more effective but comparatively safe [26]. Recently, the main immunosuppressive regimens recommended for lupus nephritis include mycophenolate mofetil, cyclophosphamide, and azathioprine [27] [28]. It was reported that adverse drug reactions such as infection, leucopenia, and liver damage occur in many patients with these current therapies [27] [28]. Therefore, more effective and safe drugs are needed. In this background, the current study aimed to evaluate the outcome of leflunomide in the treatment of lupus nephritis compared to cyclophosphamide.

In this study, total number of patients was 66, of them 32 in experimental group (leflunomide group) and 34 in control group (cyclophosphamide group). Most of the patients were in reproductive age group and female. Similar type of findings were observed in the related previous studies and reflecting the fact that SLE is common in women of reproductive age [18] [19] [20] [21]. In this current study, baseline serum creatinine in both groups was within normal limit which was consistent with previous studies [18] [19] [20] [21]. Mean 24-hr UTP, Anti-ds DNA, serum complement levels (C3/C4) and SELENA-SLEDAI scores at baseline was higher than normal limits in both groups indicating active disease processes of the patients that were supported by previous studies [18] [19] [20] [21].

After six months of treatment, 24-hr UTP, Anti-ds DNA, serum complement levels (C3/C4) and SELENA-SLEDAI scores were significantly improved in both groups. These results were compared with similar previous studies [19] [27]. Serum creatinine was stabilized or decreased in both groups, which was also an

agreement of these previous studies [19] [27].

After 6 months of induction treatment it was observed that, 25.0% patients in leflunomide group and 29.4% patients in cyclophosphamide group achieved complete remission. Partial remission rate was 31.3% in leflunomide group and 41.2% in cyclophosphamide group. Both complete and partial remission rates were higher in cyclophosphamide group, but intergroup analysis didn't show any statistically significant difference. A meta analysis performed by Cao H *et al.* that showed leflunomide was superior to cyclophosphamide in achieving remission [18]. But a couple of previous study found similar efficacy between the groups [19] [20]. Causes of lower remission rate in this current study among leflunomide group may be due to ethnic diversity, different drug dose and relatively small sample size.

In this study overall remission rate in leflunomide group was lower than that of cyclophosphamide, but mean 24-hr UTP reduction was more marked in leflunomide group, although intergroup analysis showed insignificant result. Therefore leflunomide and cyclophosphamide has comparable efficacy in reducing proteinuria, improving complement levels (C3/C4) and decreasing SELENA-SLEDAI score. These findings were supported by related previous studies [18] [19] [20] [21].

Regarding adverse events, only a few number of patients in both groups had adverse effects but there was no significant difference between them. Major adverse events observed in the patients treated with leflunomide were almost similar to those in the cyclophosphamide group and these were; elevated ALT, hypertension, infection, leucopenia and amenorrhea. We found elevation of serum ALT that occurred only in leflunomide group which was became normal level after 2 weeks with temporary discontinuation of drug. In a couple of previous studies elevation of serum ALT was found in quite high number of patients in both groups [18] [19] [21] [27]. Hypertension was also found to be associated with leflunomide group and the percentage was almost similar to that observed in a previous study [19]. In our study bone marrow suppression in the form of leucopenia and infection as in upper respiratory tract infection (URTI), urinary tract infection (UTI) were mainly occurred in cyclophosphamide group, this finding was consistent with similar previous studies [19] [27]. The current study revealed that, the percentage of amenorrhea was higher in cyclophosphamide group compared to that of leflunomide group; similar finding was observed in related previous studies [19] [27]. It was observed that, comparatively higher number of patients in control group were developed adverse drug effects than experimental group (52.9% versus 37.5%). However the adverse effects of leflunomide necessitate frequent monitoring. Patients of childbearing potential or with pre-existing infection, hypertension and liver disease should be treated with leflunomide only after prudent consideration and patient information. Therefore this current study suggested that leflunomide might be safer than cyclophosphamide in the treatment of proliferative lupus nephritis.

5. Conclusion

Leflunomide combined with prednisolone was effective in the induction treatment of proliferative lupus nephritis in Bangladeshi patients, although the efficacy was a bit lower than cyclophosphamide. Leflunomide was well tolerated and safer than cyclophosphamide in terms of infection and amenorrhea. So leflunomide can be an effective treatment option for patients who are prone to infection, women with reproductive potential and in situation where first line therapy is contraindicated. Long term randomized studies are needed to find out the efficacy and safety of leflunomide in treating lupus nephritis.

Limitation

It was a single centre study with a relatively small sample size.

Recommendation

A multi-center prospective study with large sample size should be done to compare the outcome of leflunomide in the treatment of proliferative lupus nephritis with cyclophosphamide.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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