Original Research Article

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Anti-dsDNA Response After Pulse Cyclophosphamide Therapy, with Early Proteinuria Trend as a Secondary Finding

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Abstract

Background: Lupus nephritis is a major renal manifestation of systemic lupus erythematosus and requires close monitoring of immunological and urinary response after induction therapy. Anti-dsDNA level and proteinuria are commonly used markers of disease activity and treatment response in routine clinical practice.

Objective: To assess anti-dsDNA response after pulse cyclophosphamide therapy among patients with lupus nephritis, with early proteinuria trend as a secondary finding.

Methods: This retrospective observational study was conducted at Khwaja Yunus Ali Medical College & Hospital from July to December 2025 among 34 patients with lupus nephritis or SLE-related renal syndrome receiving pulse cyclophosphamide therapy. Clinical features, anti-dsDNA levels, and proteinuria grades were analyzed. Data were expressed as frequency, percentage, median, and interquartile range, with paired non-parametric tests used for analysis. A *P*-value <0.05 was considered statistically significant.

Results: The median age was 28.0 years, IQR 24.0 to 32.0. Lupus nephritis was explicitly documented in 32 patients, 94.1%. Median anti-dsDNA decreased from 340.0, IQR 189.0 to 800.0, at baseline to 96.0, IQR 65.0 to 141.5, at 6 months. The median absolute reduction was 233.0, IQR 95.0 to 562.0, and the median percentage reduction was 66.5%, IQR 54.8% to 81.2%. All patients showed some anti-dsDNA reduction, and 28 patients, 82.4%, achieved at least 50% reduction, *P* <0.001. Median proteinuria grade declined from 2.0 at baseline to 1.0 at 1 month and 2 months. At 2 months, 33 patients, 97.1%, achieved at least one-grade improvement, and 30 patients, 88.2%, had proteinuria grade + or less, *P* <0.001.

Conclusion: Pulse cyclophosphamide therapy was associated with significant anti-dsDNA reduction and early proteinuria improvement in patients with lupus nephritis.

Keywords: Lupus nephritis, anti-dsDNA, cyclophosphamide, proteinuria, treatment response

Introduction

Lupus nephritis is one of the major organ-threatening manifestations of systemic lupus erythematosus and remains an important cause of renal morbidity in young adults, particularly in settings where late presentation, limited renal biopsy access, and inconsistent follow-up may affect treatment outcomes. Assessment of disease activity in lupus nephritis usually depends on a combination of clinical, urinary, renal function, histopathological, and immunological markers.

Among these, proteinuria and anti-double-stranded DNA antibody, anti-dsDNA, are widely used in routine clinical monitoring because they reflect renal involvement and serological activity. Engli et al. demonstrated that proteinuria severity in lupus nephritis was significantly associated with anti-dsDNA level and immune complex deposit location in the kidney, supporting the biological link between urinary and immunological disease activity.[1] In clinical practice, therefore, serial assessment of anti-dsDNA level along with urinary protein status provides a practical way to evaluate therapeutic response, especially where full renal response assessment by 24-hour urinary protein, complement level, renal biopsy, and estimated glomerular filtration rate may not always be consistently available.

Pulse intravenous cyclophosphamide has long been used as an induction therapy for active lupus nephritis, particularly proliferative disease. Annavarajula et al. evaluated proliferative lupus nephritis treated with pulse cyclophosphamide and reported favorable renal outcomes, establishing regional evidence for the effectiveness of this regimen in severe lupus nephritis.[2] Subsequent studies from South Asia have further supported the practical value of cyclophosphamide-based induction therapy. In Nepal, Sigdel et al. conducted a prospective observational study among 41 biopsy-proven lupus nephritis patients treated with six monthly low-dose intravenous cyclophosphamide pulses and steroids; complete remission occurred in 43.9%, partial remission in 39.0%, and the overall response rate was 82.9%.[3] This study also showed that baseline nephrotic-range proteinuria and severe hypoalbuminemia influenced remission, highlighting the relevance of urinary protein burden when evaluating treatment response.

Comparative studies have also placed cyclophosphamide within the broader induction treatment landscape. Sedhain et al. conducted an open-label randomized trial in Nepal comparing low-dose mycophenolate mofetil with pulse cyclophosphamide in class III to V lupus nephritis and found improvement in serum creatinine, estimated glomerular filtration rate, and 24-hour urinary protein at 6 months.[4] Sahay et al., in an Indian study comparing mycophenolate mofetil with different cyclophosphamide regimens, reported comparable remission rates across treatment arms, supporting the continued use of cyclophosphamide as an effective induction option in resource-limited settings.[5] Similarly, Wijayaratne et al. retrospectively compared low- and high-dose cyclophosphamide in class III/IV lupus nephritis from South Asia and reported no statistically significant difference in remission between the dosing approaches.[6] These studies indicate that cyclophosphamide remains clinically relevant, particularly where cost, availability, and institutional experience influence treatment selection.

Recent larger studies have continued to define the response profile of cyclophosphamide in lupus nephritis. Elaziz et al., in a multicenter retrospective Egyptian cohort of 547 patients with class III/IV lupus nephritis, found that high- and low-dose cyclophosphamide were comparable during early treatment, although high-dose therapy showed better longer-term proteinuria remission at 36 and 48 months.[7] Zheng et al., in a randomized clinical trial comparing tacrolimus with intravenous cyclophosphamide, reported a complete or partial response rate of 75.0% in the cyclophosphamide arm at 24 weeks, with anti-dsDNA conversion and proteinuria reduction assessed as part of treatment response.[8] In Bangladesh, Sejan et al. reported improvement in both proteinuria and quantitative anti-dsDNA after pulse cyclophosphamide-based therapy, providing local evidence that combined urinary and serological monitoring is feasible in routine practice.[9]

Despite these findings, limited local observational data are available on anti-dsDNA response after pulse cyclophosphamide therapy when early proteinuria trend is assessed as a secondary clinical marker. The present study was therefore conducted to evaluate anti-dsDNA response after pulse cyclophosphamide therapy among patients with lupus nephritis, with early proteinuria trend after therapy assessed as a secondary finding.

Methods

This retrospective observational study was conducted at Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh Medical Hospital over a 6-month period from July 2025 to December 2025. The study included diagnosed patients with lupus nephritis who received pulse cyclophosphamide therapy and had available baseline and follow-up clinical or laboratory records. Relevant data were collected from hospital records using a structured data extraction format. The variables included age, clinical diagnosis, associated clinical features, baseline anti-dsDNA level, 6-month anti-dsDNA level, and urine protein status at baseline, 1 month, and 2 months after therapy. Proteinuria was recorded according to dipstick grade as nil, trace, +, ++, or +++. Anti-dsDNA response was assessed by comparing baseline and 6-month anti-dsDNA levels. The primary outcome was reduction in anti-dsDNA level after pulse cyclophosphamide therapy. A reduction of 50% or more from baseline was considered a significant anti-dsDNA response. The secondary outcome was early proteinuria trend, assessed by change in dipstick proteinuria grade from baseline to 1 month and 2 months. Data were checked for consistency, coded, and analyzed using descriptive and inferential statistics. Categorical variables were expressed as frequency and percentage, while continuous variables were summarized as median and interquartile range. Changes in anti-dsDNA level and proteinuria grade over time were assessed using paired non-parametric tests, and a *P*-value of <0.05 was considered statistically significant. Ethical approval was obtained from the appropriate institutional authority, and patient confidentiality was maintained throughout the study.

Results

Table 1 shows that the study included 34 patients, with a median age of 28.0 years, IQR 24.0 to 32.0. Most patients were aged 21 to 30 years, 15, 44.1%, followed by 31 to 40 years, 12, 35.3%. Lupus nephritis was explicitly documented in 32 patients, 94.1%, while 2 patients, 5.9%, had SLE-related renal syndrome. Baseline disease activity was reflected by a median anti-dsDNA level of 340.0, IQR 189.0 to 800.0. Baseline proteinuria was predominantly moderate to severe, with ++ proteinuria in 25 patients, 73.5%, and +++ proteinuria in 8 patients, 23.5%.

Table 2 demonstrates a marked anti-dsDNA response after pulse cyclophosphamide therapy. Median anti-dsDNA decreased from 340.0, IQR 189.0 to 800.0, at baseline to 96.0, IQR 65.0 to 141.5, at 6 months. The median absolute reduction was 233.0, IQR 95.0 to 562.0, and the median percentage reduction was 66.5%, IQR 54.8% to 81.2%. All 34 patients, 100.0%, showed some reduction in anti-dsDNA, while 28 patients, 82.4%, achieved at least 50% reduction. The reduction from baseline to 6 months was statistically significant, $P < 0.001$.

Table 3 shows a clear early shift toward lower proteinuria grades after therapy. At baseline, 25 patients, 73.5%, had ++ proteinuria and 8 patients, 23.5%, had +++ proteinuria, while only 1 patient, 2.9%, had + proteinuria. At 1 month, + proteinuria became the most frequent category, 18 patients, 52.9%, while ++ proteinuria decreased to 14 patients, 41.2%, and no patient had +++ proteinuria. By 2 months, 25 patients, 73.5%, had + proteinuria, 3 patients, 8.8%, had trace proteinuria, and 2 patients, 5.9%, had no proteinuria. Median proteinuria grade declined from 2.0 at baseline to 1.0 at both 1 and 2 months.

Table 4 confirms significant early proteinuria improvement following pulse cyclophosphamide therapy. At 1 month, 26 patients, 76.5%, achieved at least one-grade improvement from baseline; this increased to 33 patients, 97.1%, by 2 months. Proteinuria grade + or less was observed in 20 patients, 58.8%, at 1 month and 30 patients, 88.2%, at 2 months. Nil or trace proteinuria was present in 2 patients, 5.9%, at 1 month and 5 patients, 14.7%, at 2 months. Compared with baseline, proteinuria grade improved significantly

Table 1: Baseline clinical and laboratory characteristics of the study patients, *n* = 34

Characteristics	Category / statistic	Result
Age group, years	18 to 20	6, 17.6%
	21 to 30	15, 44.1%
	31 to 40	12, 35.3%
	41 to 50	1, 2.9%
	Median, IQR	28.0, 24.0 to 32.0
Clinical diagnosis	Lupus nephritis explicitly documented	32, 94.1%
	SLE-related renal syndrome	2, 5.9%
Associated clinical features	Cerebral lupus	3, 8.8%
	Hypertension	2, 5.9%
	Autoimmune haemolytic anaemia	1, 2.9%
Baseline anti-dsDNA level	Median, IQR	340.0, 189.0 to 800.0
Baseline proteinuria grade	Median, IQR	2.0, 2.0 to 2.0
Baseline proteinuria category	+	1, 2.9%
	++	25, 73.5%
	+++	8, 23.5%

Table 2: Anti-dsDNA response after pulse cyclophosphamide therapy, *n* = 34

Parameter	Result
Baseline anti-dsDNA level, median, IQR	340.0, 189.0 to 800.0
6-month anti-dsDNA level, median, IQR	96.0, 65.0 to 141.5
Absolute reduction in anti-dsDNA, median, IQR	233.0, 95.0 to 562.0
Percentage reduction in anti-dsDNA, median, IQR	66.5%, 54.8 to 81.2
Patients with any anti-dsDNA reduction	34, 100.0%
Patients with ≥50% anti-dsDNA reduction	28, 82.4%
Patients with <50% anti-dsDNA reduction	6, 17.6%
P-value for baseline vs 6-month anti-dsDNA	<0.001

Table 3: Distribution of proteinuria grades at baseline, 1 month, and 2 months, *n* = 34

Proteinuria grade	Baseline	1 month	2 months
Nil	0, 0.0%	0, 0.0%	2, 5.9%
Trace	0, 0.0%	2, 5.9%	3, 8.8%
+	1, 2.9%	18, 52.9%	25, 73.5%
++	25, 73.5%	14, 41.2%	4, 11.8%
+++	8, 23.5%	0, 0.0%	0, 0.0%
Median grade, IQR	2.0, 2.0 to 2.0	1.0, 1.0 to 2.0	1.0, 1.0 to 1.0

Table 4: Early proteinuria response after pulse cyclophosphamide therapy, $N = 34$

Response parameter	1 month	2 months
≥1 grade improvement from baseline	26, 76.5%	33, 97.1%
Nil or trace proteinuria	2, 5.9%	5, 14.7%
Proteinuria grade + or less	20, 58.8%	30, 88.2%
Median proteinuria grade	1.0	1.0
P-value compared with baseline	<0.001	<0.001

at both 1 month and 2 months, $P < 0.001$ for both comparisons.

Discussion

The present study demonstrated a marked anti-dsDNA response after pulse cyclophosphamide therapy among patients with lupus nephritis. Median anti-dsDNA level decreased from 340.0, IQR 189.0 to 800.0, at baseline to 96.0, IQR 65.0 to 141.5, at 6 months. The median absolute reduction was 233.0, IQR 95.0 to 562.0, and the median percentage reduction was 66.5%, IQR 54.8% to 81.2%. All patients, 34/34, 100.0%, showed some reduction in anti-dsDNA, while 28/34, 82.4%, achieved at least 50% reduction. The reduction was statistically significant, $P < 0.001$, indicating a strong serological response after therapy.

This finding is consistent with previous evidence showing that anti-dsDNA is closely linked with lupus nephritis activity and treatment response. Manson et al. (2009) reported that anti-dsDNA antibodies were associated with renal disease activity and were lower during renal remission than active renal disease. Engli et al. also found that anti-dsDNA level was significantly associated with proteinuria severity in lupus nephritis.[1] Dall'Era et al. further showed that failure to reduce anti-dsDNA during induction therapy was associated with poorer renal outcome.[10] Therefore, the 66.5% median reduction and 82.4% ≥50% anti-dsDNA response observed in the present study support the clinical usefulness of serial anti-dsDNA monitoring after cyclophosphamide therapy.

The response observed in this study is also comparable with cyclophosphamide-based lupus nephritis studies, although the outcome definitions differ. Annavarajula et al. reported overall remission in 82.05% of patients with proliferative lupus nephritis treated with pulse cyclophosphamide.[2] Similarly, Sigdel et al. reported an overall response rate of 82.9%, including complete remission in 43.9% and partial remission in 39.0%, after low-dose cyclophosphamide induction.[3] Wijayaratne et al. reported complete or partial remission in 82% of patients receiving high-dose cyclophosphamide and 73% receiving low-dose cyclophosphamide.[6] Zheng et al. reported a complete or partial renal response rate of 75.0% with intravenous cyclophosphamide at 24 weeks, while Dong et al. reported total remission in 76.8% of patients in the cyclophosphamide arm at 52 weeks.[8,11] Compared with these studies, the present study's 82.4% ≥50% anti-dsDNA response appears favorable, but it should be interpreted as a serological response rather than complete renal remission.

The present study also showed significant early improvement in proteinuria. At baseline, proteinuria was predominantly moderate to severe, with 25 patients, 73.5%, having ++ proteinuria and 8 patients, 23.5%, having +++ proteinuria. Median proteinuria grade declined from 2.0, IQR 2.0 to 2.0, at baseline to 1.0, IQR 1.0 to 2.0, at 1 month and 1.0, IQR 1.0 to 1.0, at 2 months. At 1 month, 26 patients, 76.5%, achieved at least one-grade improvement from baseline, increasing to 33 patients, 97.1%, by 2 months. Proteinuria grade + or less was observed in 20 patients, 58.8%, at 1 month and 30 patients, 88.2%, at 2 months. Proteinuria improvement was statistically significant at both 1 and 2 months, $P < 0.001$ for both comparisons.

This early urinary improvement agrees with the broader literature supporting proteinuria

reduction as a key marker of renal response in lupus nephritis. Tamirou et al. showed that proteinuria <0.7 g/day at 12 months best predicted good long-term renal outcome, with sensitivity 71%, specificity 75%, and positive predictive value 94%.[12] Ugolini-Lopes et al. also found that 12-month proteinuria was the best single predictor of long-term renal outcome in severe biopsy-proven lupus nephritis.[13] Hanaoka et al. reported that partial renal response by 12 weeks predicted complete renal response at 3 years.[14] In this context, the present finding of significant proteinuria improvement within 1 to 2 months supports the value of early urinary monitoring. However, because proteinuria was assessed by dipstick grade, the finding should be interpreted as an early proteinuria trend rather than formal renal remission.

The present findings are also directionally similar to local evidence. Sejan et al. reported that 76.6% of Bangladeshi patients achieved urine protein ≤+ by 3 months after cyclophosphamide-based therapy, while 55.4% had anti-dsDNA <200 IU/ml by 6 months.[9] In the present study, 88.2% reached proteinuria grade + or less by 2 months, and median anti-dsDNA declined to 96.0 at 6 months. These similarities support the applicability of combined anti-dsDNA and proteinuria monitoring in Bangladeshi and comparable South Asian clinical settings.

This study has limitations. Its retrospective observational design limits causal inference. Proteinuria was measured by semi-quantitative dipstick grading rather than UPCR or 24-hour urinary protein. Renal biopsy class, serum creatinine, eGFR, complement levels, serum albumin, and urinary sediment data would have allowed a more complete renal response assessment. Despite these limitations, the study provides clinically useful evidence that pulse cyclophosphamide therapy was associated with significant anti-dsDNA reduction and early proteinuria improvement in lupus nephritis.

In conclusion, pulse cyclophosphamide therapy was associated with a significant anti-dsDNA response and early improvement in proteinuria grade. Anti-dsDNA decreased from 340.0 to 96.0 at 6 months, with 82.4% achieving at least 50% reduction. Proteinuria also improved significantly within 2 months, with 97.1% achieving at least one-grade improvement and 88.2% reaching grade + or less.

Limitations of the Study

This study was limited by its retrospective observational design, small sample size, and absence of a comparison group, which restricted causal interpretation. Proteinuria was assessed by semi-quantitative dipstick grading rather than UPCR or 24-hour urinary protein, and renal biopsy class, complement level, serum creatinine, eGFR, and serum albumin were not included in the analysis.

Conclusion

Pulse cyclophosphamide therapy results in clear improvements in blood markers and early urine tests in patients with lupus nephritis. After 6 months, anti-dsDNA levels drop significantly, and most patients show a meaningful clinical response. Proteinuria improves within the first 2 months, suggesting a good kidney outcome. These results support using routine anti-dsDNA and proteinuria tests to monitor treatment response, especially when resources are limited. Larger, forward-looking studies with more detailed outcome measures are needed to confirm these findings.

Recommendation

Pulse cyclophosphamide therapy was associated with a significant anti-dsDNA response and early improvement in proteinuria among patients with lupus nephritis. Median anti-dsDNA level declined from 340.0 at baseline to 96.0 at 6 months, with 82.4% of patients achieving at least 50% reduction. Proteinuria also improved significantly within the first 2 months, with

97.1% achieving at least one-grade improvement and 88.2% reaching proteinuria grade + or less by 2 months. These findings support the clinical usefulness of serial anti-dsDNA monitoring with early proteinuria assessment after pulse cyclophosphamide therapy in lupus nephritis.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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