DOI: https://doi.org/10.53555/nnmhs.v8i11.1430 Publication URL: https://nnpub.org/index.php/MHS/article/view/1430

MANAGEMENT TREATMENT OF PROLIFERATIVE LUPUS NEPHRITIS: A SYSTEMATIC REVIEW

Yenny Frida Setiawan*

**Faculty of Medicine, Maranatha Christian University*

Corresponding Author:-
yenny31fs@gmail.com

Abstract

One common and dire manifestation that should be looked for in SLE is the involvement of the kidneys, known as lupus nephritis (LN). Proliferative lupus nephritis is the one of types lupus nephritis which is currently still a challenge in its management. prevent nephron damage, and CKD especially end-stage kidney disease (ESKD) by administering immunosuppressive agents to improve outcomes and prognosis. This qualitative study with a systematic review approach carried out an electronic search in Medline (PubMed interface), Google Scholar, Scopus, Elsevier and Web of Science, using the keyword. Literatures were extracted, duplicate screening, and pooled analysis finally included 10 studies in the qualitative study. The clinical trial literature in the last five years includes tacrolimus, azathioprine, rituximab, cyclosporine, belimumab, leflunomide, fish oil, obinutuzumab, and voclosporin which can be combined with standard therapy. Other literature also recommends abatacept, laquinimod, ocrelizumab, sirukumab, misoprostol, plasma exchange, IV immunoglobulin, and stem cell therapy which can be used for the proliferative therapy of lupus nephritis.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that results in chronic inflammation and damage of more than one organ. It is diagnosed clinically and serologically with the presence of autoantibodies. Lupus evolved from being viewed as solely a dermatologic manifestation into an all-inclusive multisystemic disease.[1] One common and dire manifestation that should be looked for in SLE is the involvement of the kidneys, known as lupus nephritis (LN).[2] Lupus nephritis is a common manifestation of SLE. It is primarily caused by a type-3, hypersensitivity reaction, which results in the formation of immune complexes. Anti-double-stranded DNA (anti-dsDNA) binds to DNA, which forms an anti-dsDNA immune complex. These immune complexes deposit on the mesangium, subendothelial, and/or subepithelial space near the glomerular basement membrane of the kidney. This leads to an inflammatory response with the onset of lupus nephritis, in which the complement pathway is activated with a resultant influx of neutrophils and other inflammatory cells.[3] SLE is more commonly seen in women in the third decade, and lupus nephritis essentially occurs in patients 20 to 40 years old. Children with SLE appear to be at a higher risk of having renal involvement than adults. Generally, the prevalence of SLE is higher in women (female-to-male ratio of 9:1). Likewise, lupus nephritis is also more common in women; however, clinically evident renal disease with a worse prognosis is more common in men with SLE.[4] The current standardized classification system for lupus nephritis is derived from the World Health Organization (WHO) and the International Society of Nephrology/Renal Pathology Society's recommendations. The classification system is based on glomerular morphologic changes seen on microscopy, immune deposits seen on immunofluorescence, and also electronic microscopy. Class 1 is minimal mesangial lupus nephritis, in which glomeruli appear normal on light microscopy. Class 2 is proliferative mesangial lupus nephritis since mesangial proliferation is seen on light microscopy unlike class 1. Class 3 is focal lupus nephritis. Class 4 is the diffuse type in which immune complex deposits may occur in the mesangial, subendothelial, and/or subepithelial space. Class 5 is membranous LN, in which immune complex deposits are in the mesangial and subepithelial space. Class 6 is advanced sclerosing lupus nephritis in which most of the glomeruli are sclerosed.[5] Evaluating kidney function in patients suffering from SLE is important as timely detection and management of renal impairment can greatly improve renal outcomes. Proliferative lupus nephritis typically occurs three years after and usually within 5 years of the onset of SLE. The primary goal of treatment in proliferative lupus nephritis is the normalization of the kidney function or, at least, the prevention of progressive decline of kidney function. There is variability in the treatment had been noticed but none treatment steroid-independent.[6,7,8] The aim of this review is to provide update information about management treatment of proliferative lupus nephritis.

2. RESEARCH METHODS

Search Strategy

This research design is a qualitative study with a systematic review approach. Researchers carried out an electronic search in Medline (PubMed interface), Google Scholar, Scopus, Elsevier and Web of Science, using the “Proliferative Lupus Nephritis” OR “Treatment of Proliferative Lupus Nephritis” OR “Management of Proliferative Lupus Nephritis” OR “Pharmacological Therapy for Proliferative Lupus Nephritis”, between 2017 until the present time, without date restrictions. The reference list of all identified documents was scrutinized with the aim of identifying additional potentially eligible studies.

Selection Criteria

All literature was assessed for eligibility by authors. All authors assessed the title, abstract, and full text of each article identified in the search. Studies were deemed eligible for inclusion criteria and exclusion criteria. The inclusion criteria of this study are articles containing the same keywords as the research topic, the article is a full paper, the articles are published for at least in 2017, and the article must be a clinical trial or case control studies. An exclusions criterion of this study is article about editorials, reviews, and case reports, did not report data on clinical therapy for proliferative lupus nephritis, did not report clinical trial immunosuppresive in first-/second-line therapy for proliferative lupus nephritis, therapy response, side effects, and adverse events. All articles are published in all country in worldwide. When data on therapy were identified, the article was translated into English to enable data collection. Any disagreements arising during the selection assessment were resolved by discussion.

Data Extraction

Data were extracted from the included clinical trial or case control studies by authors. The data extracted included: authors, year of publications, study design, country, number of subjects, treatment regimen, primary outcome, and side effect. When unavailable data such as therapy response, we will write not available on data collection.

3. RESULT

Study selection and characteristics of included studies

A flow of studies through the analysis is presented in figure 1. After the duplicate screening, a total number of 100 articles were initially identified, 80 of the articles were excluded because they were review articles (n = 20), editorial material (n = 10), letters to editor (n=10), case report (n = 10), did not report data on therapy for proliferative lupus nephritis (n = 15), did not provide primary outcomes (n = 15), and did not provide side effects and adverse events (n = 10). Thus, the pooled analysis finally included 10 studies in the qualitative study figure 1. The essential characteristics of the included studies are presented in table 1.

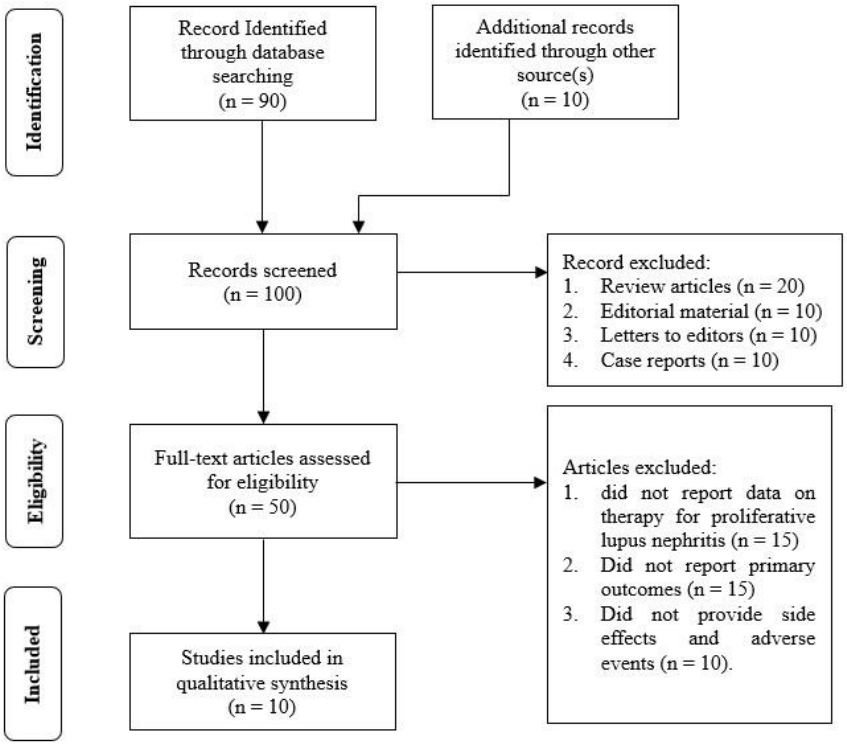

Figure 1. Study flow chart

Table 1. Summary Literature of Included Study

Author	Year	Study Design	Country	N	Treatment Regimen	Primary Outcome	Side Effect
Mehra, et al.[9]	2018	Clinical Trials	Germany	75	Low-dose (6x500 mg) vs High-dose (6x750 mg) as induction cyclophosphamide	CR was higher in high dose vs low dose (65% vs 44%) CR/PR was higher in high dose vs low dose (73% vs 50%) NR was lower in high dose vs low dose (27% vs 50%)	Most common side effect in high dose vs low dose SLEDAI (2% vs 5%) Alopecia (22% vs 5%) Leucopenia (13% vs 0%) Renal relapses (3% vs 24%)
Gadakchi, et al.[10]	2018	Retrospective case-control	Iran	67	Mycophenolate Mofetil (n = 45) vs Cyclophosphamide (n = 22)	CR was higher in Mycophenolate Mofetil (40%) vs cyclophosphamide (31.8%) PR was lower in Mycophenolate Mofetil (42.2%) vs cyclophosphamide (59.1%)	Most common side effect in Mycophenolate Mofetil vs cyclophosphamide: Infection (6.7% vs 4.5%) Abortion (6.7% vs 13.6%)
Chowdhary, et al.[11]	2022	Clinical Trials	India	15	Combination of Tacrolimus + Azathioprine + Steroid as induction therapy	CR = 53.33% PR = 26.67% NR = 20%	Most common side effect: Tremor (20%) Dizziness (20%) Vomiting (13.33%) Diarrhea (13.33%) Anemia (13.33%) Hyperglycemia (13.33%)
Goswami, et al.[12]	2022	Clinical Trials	India	22	Rituximab (1.9-g total dose)	CR = 72.7% RR (remission rate) = 90.9%	Most common side effect: Infection (27.3%) Seizure (4.5%)
Sheikholeslami, et al.[13]	2017	Retrospective Case Control	Japan	27	Low-dose cyclosporine	CR = 66.67% PR = 25.92% Treatment failure = 7.4%	Most common side effect: Hypertension (7.4%) Gastrointestinal disturbance (7.4%) Hirsutism (7.4%) Infection (7.4%)
Furie, et al.[14]	2020	Clinical Trials	United States	223	Belimumab	CR = 30% PR = 18% NR = 52%	Most common side effect: Upper respiratory tract infection (55%) Urinary tract infection (12%) Herpes zoster (7%) Bronchitis (5%) Nasopharyngitis (4%) Headache (4%) Nausea (4%)
Zhang, et al.[15]	2018	Clinical Trials	China	48	Leflunomide	CR = 23% PR = 56% Treatment failure = 21%	Most common side effect: Infection (33%) Elevated liver enzymes (18.8%) Hypertension (10%) Diarrhea (6%)
Zhang, et al.[16]	2021	Clinical Trials	China	96	Cyclophosphamide + fish oil	CR = 46.9% PR = 44.8% NR = 8.3%	Most common side effect: Infection (6.2%) Elevated liver enzymes (3.2%) Diarrhea (2.1%) Leukopenia (1.1%)
Furie, et al.[17]	2021	Clinical Trials	United States	63	Obinutuzumab	CR = 35%	Most common side effect: Urinary tract infection (23%) Bronchitis (19%) Herpes zoster (15%) Abdominal pain (11%) Infusion-related reaction (11%)
Rovin, et al.[18]	2021	Clinical Trials	United States	179	Voclosporin	CR = 41%	Most common side effect: Infection and Infestation (65%) GI disorder (47%) Nervous system disorders (26%) Skin and subcutaneous tissue disorder (24%) Musculoskeletal and connective tissue disorder (22%) Vascular disorder (21%) Blood and lymphatic system disorders (20%) Respiratory, thoracic and mediastinal disorders (15%)

4. DISCUSSION

The treatment goal of proliferative lupus nephritis is generally the same as for another lupus nephritis, namely to prevent nephron damage, and CKD, especially end-stage kidney disease (ESKD). As long as the risk of renal impairment is high in patients with proliferative lupus nephritis, immunosuppressant agents have an important role in the therapy of ISN/RPS Classes III and IV lupus nephritis. To prevent CKD, the goal of therapy in the short term is to obtain complete, or at a least partial resolution of the clinical and laboratory signs of lupus nephritis. At the time of diagnosis, the kidney damage was already very severe caused by deposits of immune complexes in the glomerulus and a tubulointerstitial inflammatory reaction. This makes patients must receive potent and high-efficacy anti-inflammatory agents such as glucocorticoids (GCs) combined with other immunosuppressive agents to reduce the autoimmune process. Immune suppression must be maintained for several years. Immunosuppressive therapy strategies in proliferative lupus nephritis were previously called the "induction phase" followed by the "maintenance phase", but the terms are now changed to "initial treatment" and "subsequent treatment".[19,20]

From some of the literature that we have searched, 10 kinds of literature report clinical trials in the last 5 years regarding the efficacy and safety of several pharmacotherapeutic options for proliferative lupus nephritis. Cyclophosphamide recommendations have been widely reported on efficacy and safety, wherein the report by Mehra, et al. (2018),[9] clinical trials compared low doses with high doses as induction therapy in proliferative lupus nephritis. In a clinical trial report given to 75 patients with class III/IV proliferative lupus nephritis, low doses (n = 38) received 6x500 mg and high doses (n = 37) received 6x750 mg/2 cyclophosphamide followed by azathioprine. The main outcomes of CR and PR showed very significant results in both patients who were given high doses compared to low doses. The most common side effects found at high doses are alopecia and leukopenia. However, high doses of cyclophosphamide can induce remission with reduced relapse. In the report by Zhang, et al. (2021),[16] clinical trials of cyclophosphamide combined with fish oil showed very good results in terms of the primary CR and PR outcomes compared to cyclophosphamide monotherapy. Improvements in hematuria, urine protein-creatinine ratio, estimated glomerular filtration rate (eGFR), and renal SLE disease activity index (SLEDAI). The incidence rate of infection also decreased in patients who were given fish oil with cyclophosphamide. The most reported side effects are infection and increased liver enzymes. Another treatment option, Mycophenolate Mofetil, has also shown good clinical trial results in proliferative lupus nephritis. In a comparative trial reported by Gadakchi, et al. (2018),[10] of Mycophenolate Mofetil with IV pulse cyclophosphamide as induction therapy, the efficacy of long-term treatment did not show significantly different results, but Mycophenolate Mofetil was still slightly superior in primary CR and PR outcomes compared to cyclophosphamide. The most common side effects are infection and abortion. The next choice of therapy is a combination of tacrolimus and azathioprine as an induction therapy for proliferative lupus nephritis reported by Chowdhary, et al. (2022).[11] In their report, the group given a combination of tacrolimus, azathioprine, and steroids was then compared to the group given a combination of cyclophosphamide and steroids as well as a combination of mycophenolate mofetil and steroids. The primary outcomes of CR and PR showed highly significant results in both the tacrolimus and azathioprine combination groups. The most common side effects were tremors, dizziness, diarrhea, anemia, and hyperglycemia. Thus, it can be considered for alternative therapy as induction therapy. The next treatment option is rituximab as induction therapy in remission cases. Goswami's report, et al. (2018),[12] conducted a comparative study between low-dose cyclophosphamide versus high-dose cyclophosphamide versus mycophenolate versus rituximab as induction therapy. The results obtained showed that high-dose cyclophosphamide and rituximab were effective in proliferative lupus nephritis patients with CR results in patients given high-dose cyclophosphamide and rituximab being 71.7% and 72.7%, respectively. Renal response (RR) was superior to high-dose cyclophosphamide (90.3%) and rituximab (90.9%). Rituximab has advantages and is very effective in cases of relapse proliferative lupus nephritis. Renal Baseline Systemic Lupus Erythematosus Disease Activity Index at baseline ($p = 0.012$) and duration of disease ($p = 0.009$) showed very significant results. The most commonly reported side effects of rituximab were infections and seizures. The next treatment option in the retrospective study reported by Sheikholeslami, et al. (2017),[13] namely low-dose cyclosporine A as therapy in cases of resistant proliferative lupus nephritis. In this study, low-dose cyclosporine was given to patients who did not respond to combination steroid therapy with mycophenolate mofetil or cyclophosphamide. The primary outcomes, namely complete and partial renal remission, showed results of 66.9% and 25.7%, respectively. Low-dose cyclosporine A can induce remission and ameliorate the SLE disease activity in patients with resistant proliferative lupus nephritis. The most commonly reported side effects were hypertension, gastrointestinal disturbances, hirsutism, and infection.

Belimumab in a clinical trial reported by Furie, et al. (2020),[14] assessed that efficacy and safety showed very significant results. Patients were given belimumab in combination with standard therapy (mycophenolate mofetil or cyclophosphamide-azathioprine) and placebo. The primary renal response was better in the belimumab group with a higher complete response than in the placebo group. Giving belimumab combined with standard therapy has a very good outcome compared to only receiving standard therapy. The most frequently reported side effects were infection, bronchitis, nasopharyngitis, headache, and nausea. The obinutuzumab clinical trial reported by Furie, et al. (2021),[17] which combined with standard therapy compared to placebo showed highly significant results. Primary outcome CRR was better in patients receiving obinutuzumab with improvements in renal response, serology, estimated glomerular filtration rate, and proteinuria. The most frequently reported side effects were infection, abdominal pain, and infusion-related reactions. The clinical trial of voclosporin which is a novel calcineurin inhibitor was reported by Rovin, et al. (2021),[18] and showed significant results for patients with lupus nephritis. Patients given oral voclosporin plus mycophenolate mofetil with rapidly tapered low-dose oral steroids compared to placebo with better primary outcomes in patients given voclosporin. Voclosporin with a combination of mycophenolate mofetil and low-dose steroids has a better outcome compared to a placebo in terms of safety. These findings can be recommended for the therapy of active lupus nephritis. The most

frequently reported side effects to include infections and infestations, GI disorders, Nervous system disorders, Skin and subcutaneous tissue disorders, Musculoskeletal and connective tissue disorders, Vascular disorders, Blood and lymphatic system disorders, Respiratory, thoracic and mediastinal disorders. The findings of the clinical trial literature for 10 recommendations for immunosuppression in patients with proliferative lupus nephritis almost showed a significant outcome, so it can be recommended as a therapy in combination with standard treatment. Another recommendation that can be given to patients with proliferative lupus nephritis reported by Tunnicliffe, et al. (2018),[21] but has not had the latest clinical trials in the last five years, including abatacept, laquinimod, ocrelizumab, sirukumab, misoprostol, plasma exchange, IV immunoglobulin, and stem cell therapy.[22,23,24,25]

5. CONCLUSION

Proliferative lupus nephritis is a manifestation of systemic lupus erythematosus which is currently still a challenge in its management. prevent nephron damage, and CKD especially end-stage kidney disease (ESKD) by administering immunosuppressive agents to improve outcomes and prognosis. Standard therapy that is currently used is still effective, such as steroids, cyclophosphamide, and mycophenolate mofetil. The clinical trial literature in the last five years includes tacrolimus, azathioprine, rituximab, cyclosporine, belimumab, leflunomide, fish oil, obinutuzumab, and voclosporin which can be combined with standard therapy. Other literature also recommends abatacept, laquinimod, ocrelizumab, sirukumab, misoprostol, plasma exchange, IV immunoglobulin, and stem cell therapy which can be used for the proliferative therapy of lupus nephritis.

6. REFERENCES

[1]. Parikh S V., Almaani S, Brodsky S, Rovin BH. Update on Lupus Nephritis: Core Curriculum 2020. American Journal of Kidney Diseases [Internet]. Elsevier Inc; 2020;76(2):265–81. Available from: https://doi.org/ 10.1053/ j.ajkd. 2019.10.017

[2]. Anders HJ, Saxena R, Zhao M hui, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nature Reviews Disease Primers [Internet]. Springer US; 2020;6(1). Available from: http://dx.doi.org/10.1038/s41572-019-0141-9

[3]. George J. Management of lupus nephritis. Journal of Association of Physicians of India. 2003;51(MAY):489–94.

[4]. Wenderfer SE, Eldin KW. Lupus Nephritis. Pediatric Clinics of North America [Internet]. Elsevier Inc; 2019;66(1):87–99. Available from: https://doi.org/10.1016/j.pcl.2018.08.007

[5]. Gasparotto M, Gatto M, Binda V, Doria A, Moroni G. Lupus nephritis: Clinical presentations and outcomes in the 21st century. Rheumatology (United Kingdom). 2020;59:V39–51.

[6]. Aggarwal A, Mehta S, Gupta D, Sheikh S, Pallagatti S, Singh R, et al. Clinical & immunological erythematosus patients characteristics in systemic lupus Maryam. Journal of dental education [Internet]. 2012;76(11):1532–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23144490

[7]. Pinheiro SVB, Dias RF, Fabiano RCG, Araujo S de A, Silva ACSE. Pediatric lupus nephritis. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2019;41(2):252–65.

[8]. Musa; R, Brent; LH, Qurie. A. Lupus Nephritis. StatPearls [Internet]. 2022; Available from: https://www.ncbi.nlm. nih.gov/books/NBK499817/

[9]. Mehra S, Usdadiya JB, Jain VK, Misra DP, Negi VS. Comparing the efficacy of low-dose vs high-dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis: a single center study. Rheumatology International [Internet]. Springer Berlin Heidelberg; 2018;38(4):557–68. Available from: http://dx.doi.org/10.1007/s00296-018-3995-3

[10]. Leyla Gadakchi, Hajialilo M, Mohammad-Reza, Nakhjavani, Azar SA, Kolahi S, et al. Efficacy and Safety of Mycophenolate Mofetil Versus Intravenous Pulse Cyclophosphamide as Induction Therapy in Proliferative Lupus Nephritis. Iranian Journal of Kidney Diseases. 2018;12(5).

[11]. Chowdhary P, Kale S, Sharma R. To study the efficacy and safety of tacrolimus and azathioprine combination as an induction therapy for proliferative lupus nephritis. Journal of The Nephrology Society. 2022;1(1):19.

[12]. Goswami RP, Sircar G, Sit H, Ghosh A, Ghosh P. Cyclophosphamide Versus Mycophenolate Versus Rituximab in Lupus Nephritis Remission Induction: A Historical Head-to-Head Comparative Study. Journal of Clinical Rheumatology. 2019;25(1):28–35.

[13]. Sheikholeslami M, Hajialilo M, Rasi Hashemi SS, Malek Mahdavi A, Gojazadeh M, Khabbazi A. Low dose cyclosporine A in the treatment of resistant proliferative lupus nephritis. Modern Rheumatology [Internet]. Informa UK Limited, trading as Taylor & Francis Group; 2018;28(3):523–9. Available from: https://doi.org/10.1080/ 14397595.2017.1352479

[14]. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. New England Journal of Medicine. 2020;383(12):1117–28.

[15]. Zhang M, Qi C, Zha Y, Chen J, Luo P, Wang L, et al. Leflunomide versus cyclophosphamide in the induction treatment of proliferative lupus nephritis in Chinese patients: a randomized trial. Clinical Rheumatology. Clinical Rheumatology; 2019;38(3):859–67.

[16]. Zhang C, Ge C, Wang J, Sun D. Fish oil enhanced the efficacy of low-dose cyclophosphamide regimen for proliferative lupus nephritis: A randomized controlled double-blind trial. Food and Nutrition Research. 2021;65(June 2021):1–7.

[17]. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Annals of the rheumatic diseases. 2022;81(1):100–7.

[18]. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet [Internet]. Elsevier Ltd; 2021;397(10289):2070–80. Available from: http://dx.doi.org/10.1016/S0140-6736(21)00578-X

[19]. Meliambro K, Campbell KN, Chung M. Therapy for Proliferative Lupus Nephritis. Rheumatic Disease Clinics of North America [Internet]. Elsevier Inc; 2018;44(4):545–60. Available from: https://doi.org/10.1016/j.rdc.2018.06.002

[20]. Dall'Era M. Treatment of lupus nephritis: Current paradigms and emerging strategies. Current Opinion in Rheumatology. 2017;29(3):241–7.

[21]. Tunnicliffe DJ, Palmer SC. Immunosuppressive Treatment for Proliferative Lupus Nephritis: Summary of a Cochrane Review. American Journal of Kidney Diseases. 2018;72(5):756–7.

[22]. Hosoda T, Hashimoto S, Sato R, Fujita M, Aizawa T, Tsugawa K, et al. Abatacept as an alternative therapy for the treatment of drug-intolerant lupus nephritis: A case of underlying monosomy 1p36 deletion syndrome. Clinical Nephrology. 2022;97(5):309–10.

[23]. Cajamarca-Barón J, Buitrago-Bohórquez J, José Emmanuel Mendoza Orozco, Segura O, Guavita-Navarro D. Efficacy and safety of intravenous immunoglobulin in patients with lupus nephritis: A systematic review of the literature. Autoimmunity Reviews. 2022;21(11).

[24]. Liu B, Ou Q, Tang Y, Fu S, Liang P, Yu Y, et al. Corticosteroids combined with doublet or single-agent immunosuppressive therapy for active proliferative lupus nephritis. Clinical Rheumatology. Clinical Rheumatology; 2019;38(9):2519–28.

[25]. Fernández-Zarzoso M, Gómez-Seguí I, Rubia J de la. Therapeutic plasma exchange: Review of current indications. Transfusion and Apheresis Science. 2019;58(3):247–53.