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LUPUS NEPHRITIS: PATHOGENESIS AND TREATMENT

[1]Alka Mariya Mathew, [2]Soumya R V, [3]Grace N Raju, [4]Prasobh G R

[1]5th Year Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

[2]Associate Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

[3]Assistant Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

[4]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic disease of unknown etiology with variable course and prognosis. Lupus nephritis (LN) is an important disease manifestation of SLE that has a significant impact on patient outcomes. Immunosuppression therapy has allowed the disease to be controlled while improving life expectancy and quality of life. Various studies conducted around the world over the last few decades have clarified the role, dose, and duration of immunosuppressive agents currently in use, as well as provided evidence for new agents such as mycophenolate mofetil, calcineurin inhibitors, and rituximab. However, there is still a need to develop new and more targeted therapies with fewer side effects. In this review, the current evidence of the treatment of LN and its evolution, and new classification criteria for SLE has been discussed. In addition, the rationale for low-dose intravenous cyclophosphamide as an induction agent, followed by azathioprine as a maintenance agent, with an emphasis on an individualized and holistic approach, has been provided.

KEYWORDS: Autoimmune disorder, immunosuppressive therapy, lupus nephritis, systemic lupus erythematosus, treatment

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, debilitating autoimmune disease involving multiple organ systems either simultaneously or sequentially with flares and remissions [1]. The word lupus is in Latin and means wolf. The Romans used the word "wolf" since the middle ages to describe the skin lesions of lupus patients that resemble lesions caused by wolf bites[1]. Nephritis was first described by William Osler as a component of SLE. Lupus nephritis (LN) is one of the most common complications in SLE patients and affects the overall outcome of these patients. Approximately two-thirds of patients with SLE will develop kidney disease at some point, which is the leading cause of death in these patients[2]. Manifestations of LN range from asymptomatic urinary disturbances to rapidly progressive end stage renal disease (ESRD)[2]. Several randomized controlled trials (RCTs) have been conducted worldwide and have added evidence to the therapeutic armamentarium, improving patient outcomes and reducing drug toxicity. Low-dose intravenous (IV) cyclophosphamide (CYC) as an induction agent followed by azathioprine (AZA) as maintenance, especially in milder LN, is the result of studies conducted in Europe and India[2].

EPIDEMIOLOGY

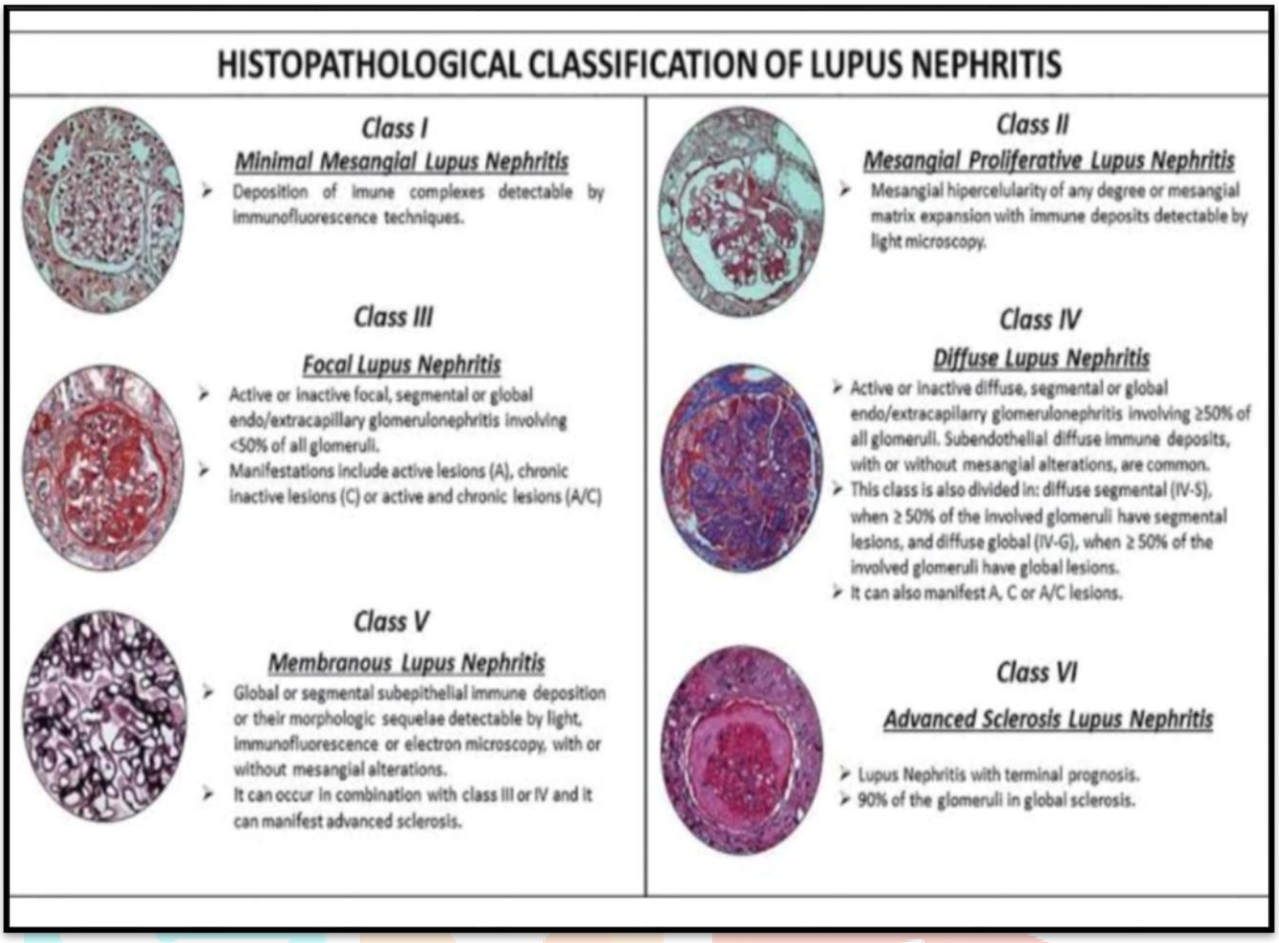
SLE prevalence and frequency vary globally according to gender, age, ethnicity, and period, which may have an effect on LN epidemiology[1]. The occurrence and prevalence of LN vary depending on the population surveyed. It has been reported that presenting with LN at a younger age is associated with more severe disease manifestations and mortality[2]. Although early-onset LN has a stronger renal response and a reduced mortality rate within the first year of diagnosis, according to a recent Japanese study. After five years following the diagnosis of SLE, the overall LN incidence was 60%[2].

PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS

The pathogenesis of SLE and LN is caused by the interaction of several factors, most notably genetic, epigenetic, and environmental factors. It is distinguished by a loss of self-tolerance that results in polyclonal antibody activation, which is traditionally manifested as positive antinuclear antibody (ANA), and a full-house pattern on immunofluorescence in renal biopsy specimens[5]. In the early stages of the disease, the innate immune system activates T-cells and B-cell activators, all of which led to the activation of the adaptive immune response. T-cells, including type 1 T-helper (TH1) cells and TH, are responsible for systemic and intrarenal B-cell activation[5]. After being activated by T-cells or the innate immune system, B-cells produce a variety of autoantibodies and cytokines. More than ten genome-wide association studies (GWAS) have been conducted in various ethnicities to identify genetic loci associated with SLE[5].

Definition and classification of Lupus Nephritis: The ACR lupus categorization criteria are proteinuria >0.5 g/day, a urine protein/creatinine ratio (UPCR) >0.5, urinary protein more than 3+ by dipstick analysis, or urinary cellular casts of >5 cells per high-power field (in the absence of urinary tract infection)[6]. The term LN describes the several types of renal injury that SLE patients experience as a result of an immune-mediated mechanism. The majority of patients also show tubulointerstitial and vascular alterations such as fibrinoid necrosis and thrombotic microangiopathy (TMA) in addition to immune complex-mediated glomerular disease[6]. The pathophysiology of nephrotic syndrome here is based on fusion of foot processes of glomerular visceral epithelial cells as seen in minimal change disease (MCD).LN was first classified by the World Health Organization (WHO) in 1974 based only on glomerular lesions, and it underwent numerous changes before arriving at the most generally used classification provided by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS)[6].

Class Abbreviated	ISN/RPS classification of LN (2003)
Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (50% glomeruli) Class V Membranous LN
Class VI	Advanced sclerosing LN
Class V	Membranous LN



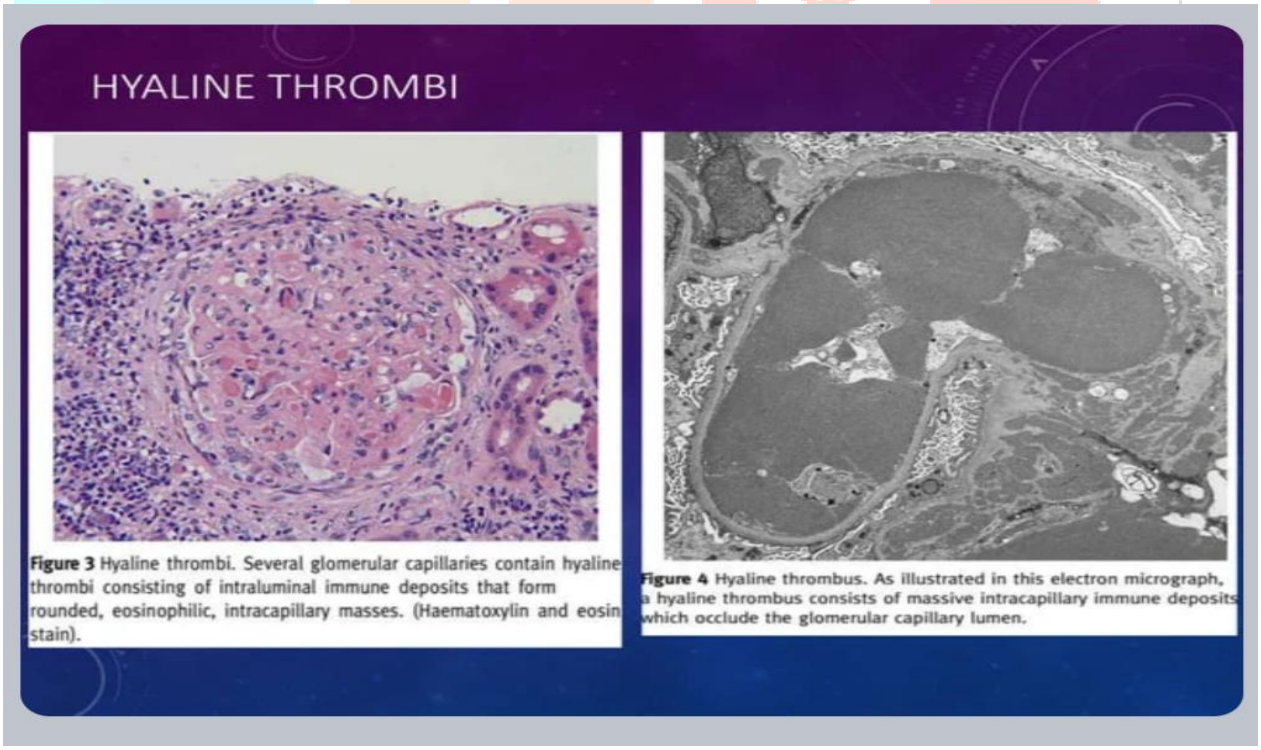


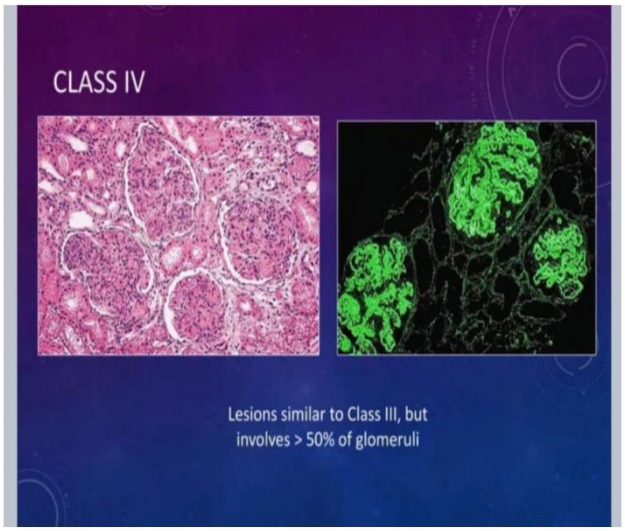
Figure 3 Hyaline thrombi. Several glomerular capillaries contain hyaline thrombi consisting of intraluminal immune deposits that form rounded, eosinophilic, intracapillary masses. (Haematoxylin and eosin stain).

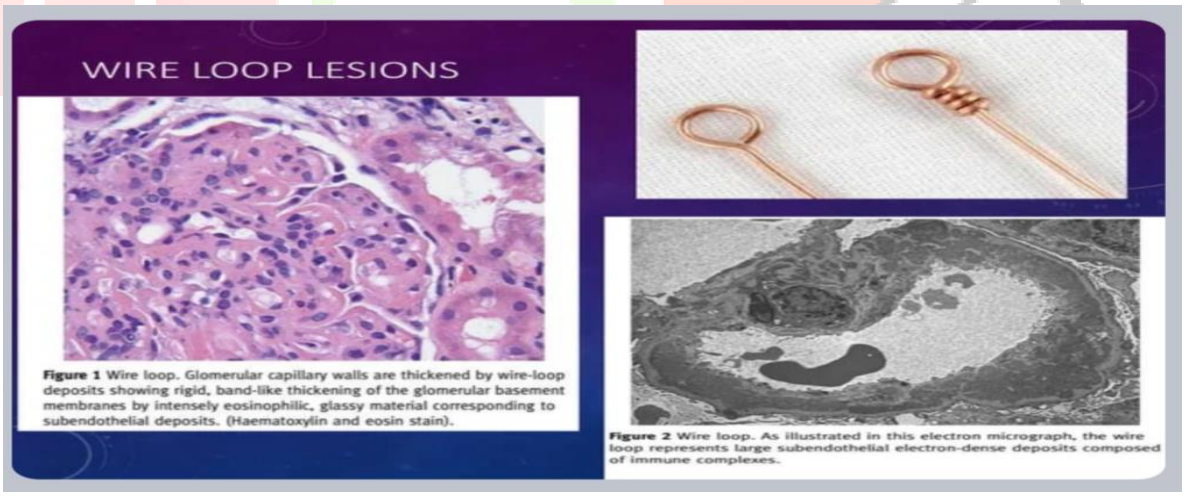
Figure 4 Hyaline thrombus. As illustrated in this electron micrograph, a hyaline thrombus consists of massive intracapillary immune deposits which occlude the glomerular capillary lumen.

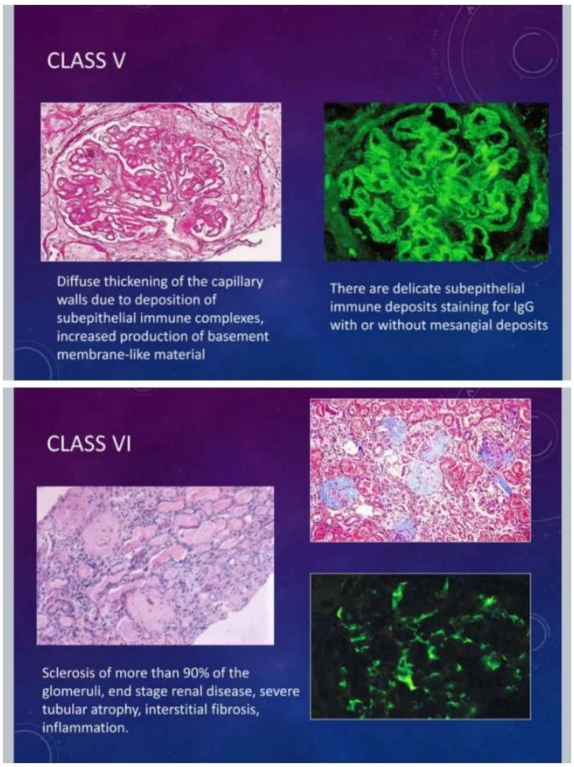

CLASS I
No structural changes by light microscopy
Delicate mesangial positivity for IgG.


CLASS III
Less than 50% of all glomeruli, segmental or global, swelling and proliferation of endothelial and mesangial cells associated with leukocyte accumulation, capillary necrosis, and hyaline thrombi; extracapillary proliferation,
Full house pattern as in class II, immune deposits also identified in tubular basement membranes, interstitial capillary walls, interstitial collagen, arterial intima, and media, Fibrinogen positivity


CLASS II
Mesangial cell proliferation, mesangial matrix expansion.
Granular mesangial positivity of all three immunoglobulins and both complements (C1q and C3) ("full house" pattern)


CLASS IV
Lesions similar to Class III, but involves > 50% of glomeruli


WIRE LOOP LESIONS
Figure 1 Wire loop. Glomerular capillary walls are thickened by wire-loop deposits showing rigid, band-like thickening of the glomerular basement membranes by intensely eosinophilic, glassy material corresponding to subendothelial deposits. (Haematoxylin and eosin stain).
Figure 2 Wire loop. As illustrated in this electron micrograph, the wire loop represents large subendothelial electron-dense deposits composed of immune complexes.



NON-PHARMACOLOGICAL MANAGEMENT OF ESRD IN LN

1. Renal Replacement Therapy: In general, hemodialysis (HD) improves clinical and serological disease activity while also lowering the need for immunosuppression, particularly in black patients. In LN-induced ESRD, HD is preferred over peritoneal dialysis (PD). Several studies have shown that patients on PD have high dsDNA antibodies, thrombocytopenia, and higher steroid requirements[7]. HD has an anti-inflammatory effect and lowers the number of T-helper lymphocytes. In haemodialyzed SLE patients, SLE flare-ups are hidden and not severe however, rash, arthritis, serositis, fever, and leukopenia occur and require specific treatment thus, careful and frequent follow-up is required in these patients[8].

2. Renal transplantation: In the USA 3% of the transplanted patients are LN-induced ESRD patients. It is critical to ensure that SLE is not present prior to transplantation[9].

PHARMACOLOGICAL MANAGEMENT OF LN

LN patients are generally hypertensive, and good hypertension control is important to prevent further renal damage and to improve protein loss. The common antihypertensives used to achieve these effects are angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)[10]. Furthermore, dietary changes significantly impact lowering blood pressure and controlling hyperlipidaemia. To prevent further kidney damage, it is critical to avoid nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs). Pregnancy is a trigger for worsening of kidney function in LN patients, and pregnancy should be avoided especially when the SLE is active because some medications might be a teratogen, and the risk of abortion is high. As a result, a woman should not conceive while her SLE is active and requires these teratogenic drugs[10].

A. Immunomodulation agents

HCQ (Hydroxychloroquine): According to some data, HCQ improves nephrotoxic outcomes. HCQ lowers the risk of tubulointerstitial inflammation, and one HCQ treatment resulted in a complete response[22]. HCQ treatment significantly reduces LN progression to CKD and/or ESRD. It has been reported that removing HCQ from the LN management plan is associated with a twofold increase in death, ESRD, renal flare, or the need for rescue therapy during the LN management maintenance phase[22].

B. Immunosuppressive agents

- Cyclophosphamide (CYC) at high doses: LN treatment is divided into two phases: induction and maintenance. Induction therapy is the initial therapeutic regimen used to try to induce remission of active disease. The goal of induction is to achieve rapid results[11].
- Azathioprine (AZA): Azathioprine (AZA) is a purine analogue that inhibits DNA synthesis and is most effective in rapidly proliferating cells. It has been widely used in organ transplantation and the treatment of various autoimmune diseases. As a result of early NIH trials in which AZA performed worse than iv CYC, it was not approved for use as induction therapy in LN. It did, however, emerge as a drug of choice as a maintenance agent in LN due to its efficacy and safety than long-term iv CYC use[12].
- Mycophenolate mofetil (MMF): In the early twenty-first century, Mycophenolate mofetil (MMF) was introduced as a therapeutic option for LN[12].
- Low-dose cyclophosphamide (CYC): Randomised controlled trial with 90 patients having proliferative LN receiving either standard six-monthly pulse of CYC (0.5- 1 g/day) followed by every third monthly infusion or to a shorter treatment course consisting of a fixed dose of 500 mg iv CYC every two weeks for six doses (total dose, 3 g) and AZA maintenance therapy (2 mg/kg/ day)[13]. The shorter regimen was equally efficacious, had less toxicity with significantly less severe and total infections, and follow-up for 10 years showed no differences in outcome between the treatment groups[13].
- Calcineurin inhibitors (CNIs): Using their knowledge of transplant medicine and proteinuric glomerular diseases, researchers used CNIs as an induction and maintenance agent in both proliferative and membranous LN[14].

C. Biological Agents

- Rituximab (RTX): RTX is a chimeric anti-CD20 monoclonal antibody made up of murine variable regions against CD20 and the human IgG Fc constant region. Rovin et al studied the safety of RTX in a randomised, double-blind, placebo-controlled phase III trial in patients with LN treated concomitantly with MMF and corticosteroids. They discovered that while RTX reduced peripheral CD19 B-cells, anti-dsDNA titres, and C3/C4 levels, it did not translate into better clinical outcomes. Furthermore, it did not result in any new safety concerns[15].
- Belimumab: For the last 50 years, Belimumab has been the only Food and Drug Administration (FDA)-approved drug for SLE. This was the outcome of the clinical efficacy and safety demonstrated in two

large-scale phases III RCTs, involving 1684 patients with lupus, conducted in people across various ethnicities and continents[16].

The following substances are also being looked into in SLE and LN: When compared to steroids alone, Mizoribine (an imidazole nucleoside that inhibits de novo purine synthesis) did not provide any advantages[18]. Leflunomide, an inhibitor of de novo pyrimidine synthesis, has primarily been used in non-renal SLE, but in its present use, it did not provide any advantages over other immunosuppressive drugs and was instead linked to a variety of side effects like thrombocytopenia, skin rash, diarrhea, and hepatotoxicity. The use of leflunomide in LN was found to be as effective and safe as CYC at least in the short term and also in refractory LN[18].

However, at present, it does not far better than current first-line immunosuppression in LN but has a role to play in refractory/resistant disease. Malignancy and autoimmune disease have been linked to the mTOR (mammalian target of rapamycin) pathway. Investigators used rapamycin an inhibitor of mTOR in a murine model of LN, NZBW/ F1 [F1 hybrid between the New Zealand Black (NZB) and New Zealand White (NZW) strains] female mice and found it effective in prolonging survival, and maintaining normal renal function, normalizing proteinuria, restoring nephrin and podocin levels, reducing anti-dsDNA titres, ameliorating histological lesions[19]. There are anecdotal reports of the success of plasmapheresis in addition to current immunosuppression, but these are mainly in patients with TMA associated with diffuse alveolar hemorrhage. Plasmapheresis can also be combined with intravenous immunoglobulin, particularly in cases of refractory LN or active life-threatening SLE and infection[19]. There are uncontrolled studies on the use of intravenous immunoglobulin as initial therapy in LN usually along with steroids with equivocal outcomes although with steroid-sparing effect[19].

Evidence-based Treatment for Lupus Nephritis

Guidelines are published by groups like the Kidney Disease: Improving Global Outcome (KDIGO), The European League Against Rheumatism, the American College of Rheumatology (ACR), and the European Renal Association- European Dialysis and Transplant Association (EULAR/ERA-EDTA) [20]. Overall, renal biopsy should be used to guide immunosuppressive therapy, with the goal of achieving complete renal response (proteinuria 0.5 g/24 h with normal or nearly normal renal function). Class I, Class II (with proteinuria 3 g/day), and Class VI LN do not require any treatment from a renal point of view but should be treated as per extra-renal reasons, according to the ISN/RPS classification of LN[20]. All of these important recommendations suggest using CYC or MMF in combination with steroids in Class III/IV LN to suppress the immune system. According to ACR recommendations, MMF should be preferred in Class III/IV LN, particularly in African Americans and Hispanics[17]. KDIGO and EULAR recommendations propose a 3 g/day dosage objective for MMF, however, the ACR only advises 2 g/day for Asians[20]. While KDIGO advises using any of CYC/ MMF/AZA/CNI combined with steroids in Class V LN, both ACR and EULAR/ ERA-EDTA support using steroids plus MMF in Class V LN with nephrotic range proteinuria. For the

treatment of lupus podocytopathy, which has ultra-structural homology with minimal change disease (MCD), steroids in accordance with MCD are suggested[20].

Refractory and relapsing lupus nephritis

Despite the use of aggressive immunosuppression, a few patients of LN may not respond. Around 20-70 percentage of patients with LN are resistant to first-line immunosuppressive therapy. There is no universally agreed-upon definition of resistant/refractory LN. Patients who do not achieve a partial response after 6-12 months or a complete response after two years of treatment should be switched to an alternative drug[21]. It is also advised to switch to a different agent if there are signs of deterioration in the very early stages of treatment. An alternative agent could be RTX alone or in combination with other immunosuppressive medications, or any of the extended courses of CYC or CNI[21].

LN is a relapsing disease that requires plasmapheresis or multitarget therapy. Renal relapse/flare is defined as the return of active urine sediment or proteinuria greater than 0.5 g/day, as well as an increase in serum creatinine. The average rate of renal relapse after reduction or cessation of immunosuppression varies from 5 to 15/100 patient years, in different series within first five years of attaining remission[21]. Relapses should be treated with the same induction agent that was effective on the previous occasion unless contraindicated (high dose CYC), and a repeat renal biopsy should be considered if there is uncertainty about the diagnosis or the chronicity of the disease. Serum creatinine and proteinuria are the two most crucial biomarkers to track the development of LN, and the disappearance of proteinuria is the key indicator of kidney survival[21]. In addition, patients should have their blood pressure, body weight, estimated glomerular filtration rate (GFR), serum albumin, urine sediment, serum C3 and C4, serum anti-ds DNA antibody levels, and complete blood count frequently checked during each visit. Clinically, lupus can be either chronic, dormant, or relapsing. 3-6 months for the rest of their lives[21].

Ancillary Treatment in Lupus Nephritis

KDIGO and EULAR/ERAEDTA state that HCQ should be administered to all LN patients unless it is contraindicated. According to EULAR/ERAEDTA, ACE/ARB should be administered to all patients with LN acetyl-salicylic acid if antiphospholipid antibodies are present, statins if low-density lipoprotein cholesterol (LDL-C) is greater than 100 mg/dl, and oral anticoagulants if antiphospholipid antibody syndrome (APLAS) or nephrotic syndrome with 2 g/dl of serum albumin[22]. In accordance with risk and age, non-live vaccines should also be administered to patients. They ought to be given supplements as well as vitamin D and calcium while keeping a close eye out for metabolic bone disease[22].

Plasmapheresis should be administered to patients who have a diffuse alveolar hemorrhage, LN, and TMA. Sun exposure, particularly exposure to ultraviolet light (UV), is a well-known component that can cause cutaneous lupus to flare up[23]. However, many anecdotal reports have revealed that sun exposure can also exacerbate non-cutaneous lupus, including LN. The theory behind this phenomenon is that exposure to UV

light causes epidermal DNA to break down more quickly, which increases its antigenicity and causes more antibodies to develop and immune-mediated organ damage. Sun protection is therefore recommended for those who have LN[23].

Lupus nephritis and antiphospholipid antibody syndrome (APLAS)

APLAS is characterized by the presence of antibodies against phospholipids, frequent thrombotic episodes, and/or foetal loss. Compared to the general population, patients with SLE experience thrombotic events at significantly greater rates[24]. Antiphospholipid antibodies are the main cause of the pro-thrombotic state in SLE; however, other conventional factors, including hyperlipidemia, aging, diabetes, hypertension, smoking, male sex, disease activity, and medications like corticosteroids, also contribute to, initiate, or propagate the pro-thrombotic state of SLE[24]. The most typical cause of APLAS is SLE. A common manifestation of renal involvement in APLAS is antiphospholipid syndrome nephropathy (APSN), which is characterized by microthrombi in the acute phase and signs of recanalization and fibrous intimal hyperplasia in the chronic phase. Patients with SLE, either with or without LN, may develop APSN. APL antibodies are linked to worse renal function outcomes. Similarly to this, about 20–30% of SLE patients show histological lesions that are compatible with APSN. In this case, a biopsy diagnosis is required because anticoagulation is used to treat APSN but immunosuppression is needed to treat LN[24].

Pregnancy in Lupus Nephritis

Pregnancy is linked to lupus accompanied by a higher risk of preeclampsia, early labour, thromboembolic events, infections, mother-specific LN flare, intrauterine growth restriction, neonatal lupus, and preterm birth. Congenital heart block (CHB) is more likely when Ro and La antibodies are present, necessitating careful monitoring during pregnancy[25]. Typically, the CHB develops between weeks 18 and 24 of gestation. Pregnancy may be planned in stable patients with inactive lupus, UPCR 50 mg/mmol over the prior six months, and GFR that should preferably be >50 ml/min, according to EULAR/ ERA-EDTA and KDIGO. The usage of medications like CYC, MMF, ACEI, and ARB should be avoided while HCQ, low-dose prednisone, AZA, and CNI are all acceptable medicines to take while pregnant. During pregnancy and the preconception period, the medication shouldn't be scaled back[25]. In the first half of pregnancy, the patient should be regularly monitored every four weeks, and in the second half of pregnancy, every one to two weeks. Consider using acetylsalicylic acid to lower the risk of preeclampsia. In pregnant lupus patients, the administration of HCQ has been demonstrated to reduce a variety of maternal and foetal complications[25].

Most commonly, remission of extrarenal symptoms of SLE is accompanied by the progression of LN to ESRD in most patients[26]. Despite vigorous treatment, 10–30% of patients with LN develop ESRD over a 15-year period. Recent US data show that over the past ten years, the overall rates of ESRD in LN have ceased rising. EULAR/ ERA-EDATA states that although HD is linked to problems related to vascular thrombosis, particularly with antiphospholipid antibodies and an elevated likelihood of infections in later

modalities, the outcomes of patients with LN-associated ESRD on HD or peritoneal dialysis are equal[26]. The majority of lupus patients with ESRD can get the optimum rehabilitation with a renal transplant. Both lupus patients and non-lupus patients receiving transplants have comparable allograft survival rates[27]. Transplantation should be carried out after lupus has been dormant for a minimum of six (3–12) months[27]. Although people with antiphospholipid antibodies have a higher chance of graft failure, the outcomes are better for living donor. Recurrence of LN after kidney transplant is infrequent (2–11%) and typically does not affect the long-term graft outcome[27].

CONCLUSION

With the available therapies, LN has changed from being an uncontrollable disease to one that is curable and involves a trade-off between enhanced results and unfavorable therapy-related consequences. Despite the fact that lupus is known to react differently in different people, the use of kidney biopsy assessments for treatment has made therapies practically identical worldwide diversely between races and ethnic groups. Along with a steroid tapering regimen, low-dose intravenous CYC or MMF has been recommended as an induction drug for proliferative LN. However, in individuals with crescentic LN accompanied by loss of GFR, high-dose intravenous CYC or MMF may be preferable. For patients from the Indian subcontinent, a target dose of MMF of 2 g/day during induction and 1 g/day during maintenance may be sufficient. In numerous studies conducted throughout the world, AZA and MMF have performed nearly equally as maintenance agents in terms of outcome factors related to safety and efficacy.

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