REVIEW

Lupus Nephritis: Pathogenesis and Treatment Update Review

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Abstract:

Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE). LN is a leading cause of morbidity and mortality in SLE patients. LN presents with various symptoms and signs, ranging from asymptomatic renal involvement to End-Stage Renal Disease (ESRD). The pathogenesis of LN is not clearly understood, however, there are extra and intra-renal underlying factors that have been postulated in LN pathogenesis. Renal biopsy is crucial to stage LN and to rule out other causes. Histopathological studies have shown six different types of LN. Knowing the histopathological lesion, chronicity and the disease activity are essential to plan the LN treatment and to predict the outcome. There are different regimens for treating LN. In this review, LN pathogenesis and new advances in treatment will be briefly reviewed.

Introduction

LN is one of the most serious manifestations of SLE. LN affects 30% to 50% of all SLE patients, and it causes end-stage renal disease (ESRD) in 20% of affected patients (1). LN associates with 4 folds increase in morbidity and mortality rate (2). About 50-60% of adult SLE patients have clinical features of kidney involvement during the SLE disease course (3). Other reports noted kidney involvement in SLE patients occurs in up to 40% of patients (4). LN occurs commonly within 5 years of the SLE diagnosis or sometime later (5). Characteristically, LN presents with hypertension, proteinuria, however, chronic kidney disease (CKD) and ESRD are not uncommon complications. The first presentation of LN is a reduction of estimated glomerular filtration rate (eGFR)

and/or significant proteinuria >500 mg/day in about 30% of cases. The degree of eGFR reduction and proteinuria at presentation may help to predict the severity of the histopathological changes (6), however, it is not always precise (7).

Silent LN occurs, manifesting mostly by an increase of blood pressure with normal serum creatinine and urine analysis (8). Renal biopsy is the gold standard for LN diagnosis and is needed to assess the histological stage, chronicity, and activity that are required before initiating the long-term treatment (9). Despite the advancement of SLE treatment, about 20% of LN patients develop ESRD commonly after 10 years (10). LN pathogenesis is an immune complex-mediated process, however, other factors have an essential role in LN pathogenesis (11). The role of complement, autoantibodies, apoptosis, and the adaptive immune system in the pathogenesis of LN has been speculated. In this update review, the suggested pathogenetic mechanism(s) and treatment updates will be discussed.

Epidemiology

There are worldwide variations in the frequency and prevalence of SLE that vary with sex, age, ethnicity, and time that can affect LN epidemiology (12). Depending upon the population surveyed, the occurrence and prevalence of LN varies (13).

At presentation, Class II LN is the most prevalent (56%) followed by Class II (26%), and then Class III (18%) (14). It was reported that earlier age of LN presentation associates with more severe disease manifestations and earlier mortality (15). However, a new Japanese study reported that early-onset LN has a better renal response and lower mortality rate during the first year of the diagnosis (16). The overall LN incidence was 60% after 5 years of post-SLE diagnosis (17).

LN appears to be more prevalent in certain ethnic groups. It was reported that 45% of African Americans, 42% of Chinese, and 30% of Caucasian SLE patients had evidence of renal involvement (18). Another multi-ethnic USA cohort study reported that renal disease occurred in 51% of Africans and 43% of Hispanics and 14% of Caucasians SLE patients (19). Other reports noted that 31% of new-onset SLE patients had an active renal disease at first presentation (18).

It was reported that kidney outcome and mortality are worse in African and Hispanic patients than Caucasian patients, and there are differences in prognosis among different ethnicities. Black and Hispanic American patients have the worst outcomes, and they commonly progress to kidney failure than white patients (3),. Furthermore, the Black and Hispanic patients seem to develop worse histopathological changes, more proteinuria, and higher serum creatinine levels than white patients at LN diagnosis. Moreover, anti-Sm, anti-Ro, and anti-ribonucleoprotein autoantibodies that are associated firmly with LN, are more often positive in black than white patients (3). The justifications for the racial and ethnic differences are not well-understood, however, genetic and socioeconomic factors may have a role (3). A study that had compared early-onset and late-onset LN in an Asian population reported that early-onset LN patients had a lower mortality rate than late-onset LN during 6 and 12 months follow up (19). Ugolini-Lopes et al reported that there is no significant difference in disease severity and long-term prognosis (20).

Pathogenesis of LN

LN pathogenesis is essentially related to the site of anti-double-stranded DNA antibodies (anti-dsDNA, or anti-DNA) immune deposit formation (21). Anti-DNA immune complex consists of DNA and anti-DNA, although the immune complex may also contain chromatin, C1q, laminin, Sm, La (SS-B), Ro (SS-A), ubiquitin, and ribosomes (22). Anti-DNA antibodies can combine directly with the glomerular basement membrane (GBM) and mesangium parts (23). If the immune deposits occur in the mesangium and subendothelial space, they will be adjacent to the GBM and glomerular tuft space. This deposition activates complement classical pathway that enhances the chemoattractants (C3a & C5a) production, triggering migration of neutrophils and mononuclear cells into glomerular tuft space. These changes cause a mesangial or focal or diffuse proliferative glomerulonephritis changes which are present by red cells, white cells, and cellular and granular casts, proteinuria with rapid renal function deterioration. When the immune complex deposits are landed in the subepithelial space, it can activate the complement cascade with inflammatory cell influx into the subepithelial space, causing nephrotic range proteinuria and membranous nephropathy histopathological lesions. Another important determinant of the site of the immune complex formation and deposition is related to both the charge of the antibody and its antigen-binding region. The antibody may attach to antigens at different glomerular capillary wall sites, causing different histologic and clinical manifestations (24). Some data suggest that intraglomerular membrane-associated nucleosomes are targeted by anti-dsDNA autoantibodies (25). There is evidence that some patients have anti-DNA antibodies but no nephritis, and Anti-DNA can cause nephrotoxicity without immune complex formation. Anti-DNA antibodies can bind to human mesangial cells in vitro and induce proinflammatory substances production, increasing the risk of LN (26).

Neutrophils and neutrophil extracellular entrapment may add to antigen-specific autoantibody production, inducing inflammation, endothelial damage, and interferon-alpha formation inside the renal tissue (6). Furthermore, Immune (small i) complex deposition can activate an inflammatory response. Immune complex to endothelium can lead to proinflammatory leukocytes recruitment, promoting autoimmune injury (27). Activated glomerular cells, infiltrating macrophages, and T cells cause inflammatory cytokines, involving tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), tumor growth factor-beta, interferon-gamma, chemokines, and platelet-derived growth factor release (28). Additionally, activated platelets induce also mesangial cell proliferation, enhancing further damage (29).

Different genetic factors predispose patients to the development of LN (30). There is evidence that LN is more common and severe in certain ethnic populations, indicating genetic factors in LN pathogenesis (31–33). Macrophages immunoglobulin receptor alleles Fc-gamma-RIIa-H131 polymorphisms have a link with susceptibility to LN (33), however, another study reported that there is not any link (32). Other reports found strong links between the Fc-gamma-RIIIa-F158 receptor allele and Fc-gamma-RIIIb polymorphisms and lupus nephritis (32,33). Furthermore, LN due to glomerulosclerosis in African Americans has APOL1 gene variants (34).

A. Extrarenal pathogenic mechanism (Fig 1)

A-1. Cell Death and Dead Cell Handling

SLE patients have unusual genetic variants that may alter apoptosis of the dead cell (35), the complement system and/or phagocytes (36). Neutrophils commence what is called NETosis. Naturally, the neutrophils are removed from the circulation after 6-8 hours (37). The inflammatory process activates the neutrophil that has diverse complexed functions such as apoptosis that diverts to the neutrophil extracellular trap, leading to cell death process called NETosis (38). It is thought that the released nuclear particles of the damaged cells are recognized as foreign proteins by the immune system in SLE patients. The activated immune cells damage most of the body organs including the kidneys, causing LN.

A-2. Environmental factors for LN development

Bacterial and viral infections stimulate SLE activity. Bacterial infections cause a transient expansion of autoreactive lymphocyte clones and accelerate intrarenal immune cells, promoting the severity of proteinuria and kidney damage (39). Ultraviolet light in SLE patients causes keratocyte death (40), and estrogen and progesterone accelerate the sex hormone-dependent immunoregulatory pathways (41). Fig (1)
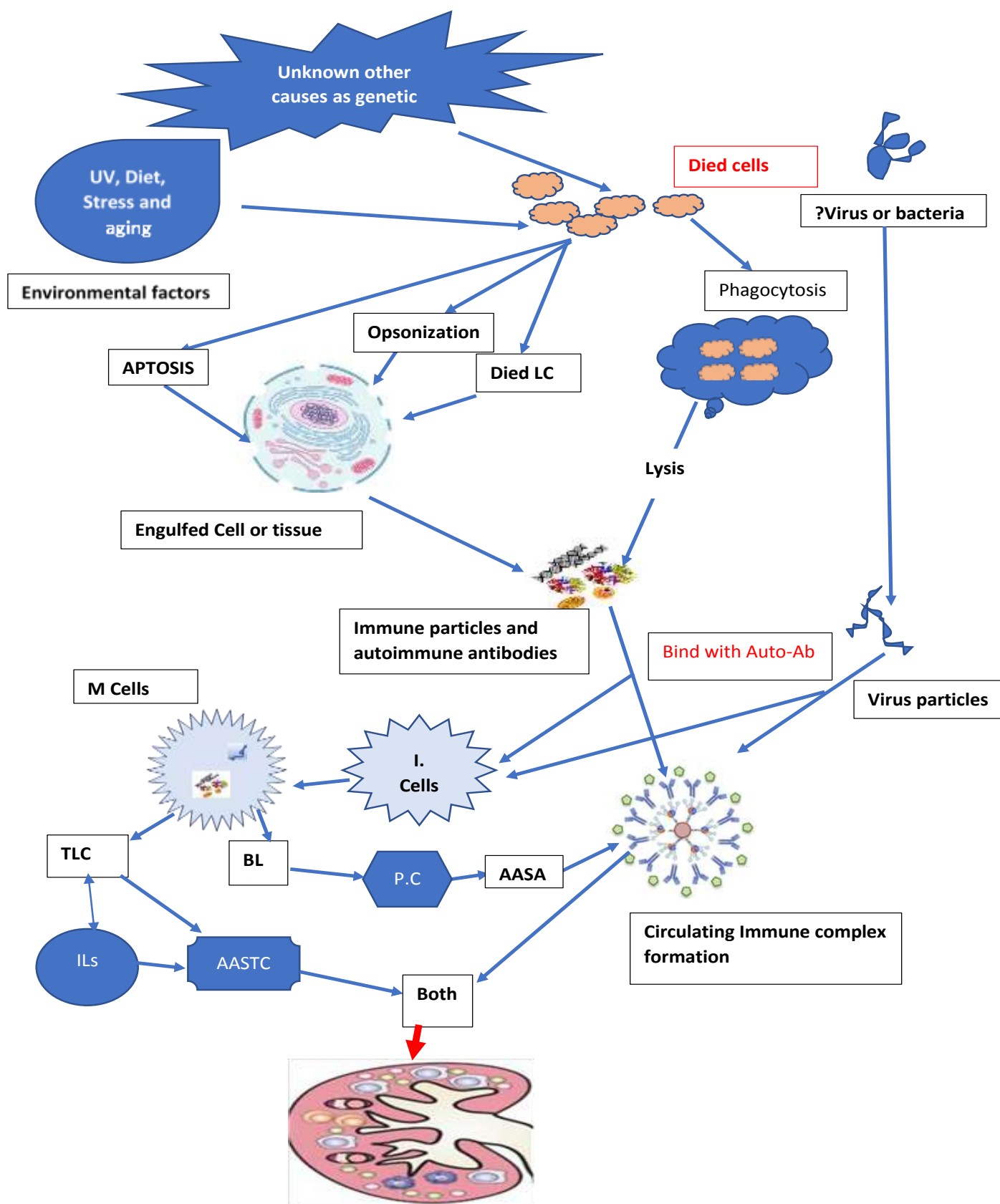
Fig 1. Extrarenal mechanism of Lupus Nephritis

Lymphocyte (LC), Immature mother cells (I. Cells), Mature mother cells (M cells), B-lymphocyte (BL), Plasma cell (P.C), Interleukins (ILS), Auto-Antigen-Specific-T Lymphocytes (AASTC), Auto-Antigen-Specific-Antibodies (AASA).

B. Intrarenal Pathogen

B-1 Immune complex

LN pathogenesis involves an auto- nonspecific activation of B cells, leading to immune globulins formation in the kidney tissues. (42) Furthermore, it seems that B cells have pathogenic effects more than antibody formation such as autoantigen presentation to the stimulated T cells, and inducing local proinflammatory effects (43).

Mesangial, endothelial, subendothelial and peritubular capillaries immune complex deposition site has a significant role of LN severity (44). In class I&II LN, the deposition is in the mesangium, class III and IV LN at the endothelial regions, and in class V, the immune complexes deposition is in the subepithelial tissues (45).

Anti-DNA antibodies from the damaged cells activate endothelial and mesangial cells via different mechanisms. The formed antibodies are directly engulfed by renal cells. This process involves cross-reactivity with a-actinin or annexin II on mesangial cells (46), damaging the interstitial cells, however, this theory was not supported by some reported data (47). It was reported that complement activation and its released factors lead to immune complex deposition, promoting inflammation and immunopathology reactions, opsonization, and lupus autoantigens removal from the extracellular space. All these responses are reduced in complement system deficiency (48).

Immunostimulatory nucleic acids stimulate the glomerular endothelium, mesangial cells, and macrophages to produce large amounts of proinflammatory cytokines and IFN-a and IFN-b (49). The significance of IFN intraglomerular signaling is not well understood, although it can cause kidney damage in the LN, leading to changes in tubuloreticular structures. These tubuloreticular changes may lead to ultrasonic changes in about 95% of NL patients. These ultrasound changes are abnormal renal size and change in cortical echogenicity, correlating perfectly with the degree of kidney damage caused by LN (50).

B-2. Repair of the damaged tissue

Progression of CKD in LN is related to degree of renal parenchymal cell damage, and the amount of renal fibrosis. Focal glomerular tuft necrosis causes parietal epithelial cells migration into the glomerular tuft that forms an extracellular matrix, producing FSGS which may progress to global glomerulosclerosis (51). Parietal cell stimulation by mitogens as fibrinogen accounts for cellular glomerular crescent formation to occupy the urine space by uneven glomerular tuft cells proliferation (52). In stage V LN, the parietal epithelial cells polarity is lost due to the increased honeycombing of Bowman's space, turning the cellular crescents into fibrocellular crescents with global glomerulosclerosis.

Histopathological classification of LN

Renal biopsy is needed to know which class the patient has and to plan the treatment. Despite the diversity of recommendations and the indications of renal biopsy in LN, some authors commending to carry out the renal biopsy if there is not contraindications (53). During 2004, nephrology, pathology, and rheumatology scientists tried to agree upon a uniform classification for LN. The

classification seems more informative than the 1982 modified WHO classification (44). Six different histological lesions of LN were proven by the International Society of Nephrology (ISN) classification system. It was reported that serological and sedimented urine markers may give a hint to the underlying histological changes, however, none of these markers eliminate the significance of the renal biopsy to assess the chronicity and activity of the LN (54).

A. Class I (Minimal mesangial LN)

This lesion affects primarily children generally in non-SLE patients. In SLE patients, this class is not usually diagnosed early, because it usually presents with mild transient proteinuria or even normal urine analysis. These patients rarely require renal biopsy. Histologically, there are mesangial immune complex deposits that are immunofluorescent positive, and these deposits can be detected only by electron microscopy.

B. Class II (Mesangial proliferative lupus nephritis)

Mesangial hypercellularity (of any degree) and/or mesangial matrix expansions are detected by light microscopy. By electron microscopy, there are subepithelial or subendothelial deposits. Class III (Focal LN)

This class is subdivided into focal and diffuse. When half or less of the biopsied glomeruli are involved then known as focal LN type, whereas diffuse class III subtype has > 50% of glomeruli are affected by light microscopy examination. Immunofluorescence microscopy (for IgG and C3) reveals almost uniform involvement in >50% glomerular damage (55). Hematuria and proteinuria, hypertension, reduced eGFR, and/or nephrotic syndrome are usually present in different combinations.

Class IV (Diffuse LN)

Class IV lupus nephritis is the worst histologic type of LN. Microscopically, there are glomerular and interstitial lesions with varied degree of sclerosis as well fibrosis. Reduced eGFR, proteinuria and hypertension with generalized oedema might be the presenting features.

E. Class V (membranous LN)

In this class, massive proteinuria and features of nephrotic syndrome are characteristic presentations (56). Histologically, there is a characteristic diffuse thickening of the glomerular capillary wall on light microscopy with subepithelial immune deposits (either global or segmental involvement) on immunofluorescence or electron microscopy.

F. Class VI (Advanced sclerosing LN)

Class VI is characterized by generalized glomerular sclerosis in > 90% of the glomeruli. It is the result of all classes of LN progression. Patients have usually slowly progressive renal function impairment with proteinuria and almost normal urine routine sediment. Identification of this class of lesions is essential, while it will not benefit from immunosuppressive therapy.

LN is a heterogeneous disease and may present with different combinations of clinical and laboratory features. Each LN patient has his/her variable features, but notably, different clinical settings and histopathological patterns may present in a single patient during the disease progression.

Treatment of LN

The published treatment regimens of LN by the European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) aimed for a full renal response during 12 months, although, more than 12 months of treatment might be required when the proteinuria presents before initiating the treatment (53). Despite the negative effects of age, sex, ethnicity, and histological findings, LN complete response to the immunosuppressive drugs was reported at 6 and/or 12 months, leading to better renal outcomes and less mortality rate (8,16). In general, in recent decades, while the prognosis of LN has improved due to the availability of advanced diagnostic and treatment facilities (6), there are still therapeutic challenges. A collaborative approach between rheumatology and nephrology teams is necessary to obtain better results. LN treatment response is clinically defined and usually stratified into complete, partial, and no response (3).

Immunosuppressive therapy is usually required for patients with active diffuse and focal proliferative LN (class III&IV LN) (57), but in class I and minimal mesangial and mesangial proliferative LN is not always indicated. The prognostic and therapeutic responses depend on the degree of LN activity (active inflammation) and chronicity (glomerular scarring, tubulointerstitial fibrosis, and atrophy), although it is usually not applicable in all cases (57). Some reports have shown differences in LN severity and LN outcomes between black African-American or Afro-Caribbean and Hispanic populations compared to non-Hispanic white patients, as well as the response to immunosuppressive treatment (19,58).

Table 1. Features of Chronicity and Activity of Lupus Nephritis.

Disease activity	Disease chronicity
A-Glomerular changes	
1. Endocapillary hypercellularity +/- leukocyte infiltration and decreased the lumen of the capillary	1. Glomerular sclerosis (segmental or global)
2. fibrinoid necrosis & Karyorrhexis	2. Cellular crescents
3. Crescents formation	
4. Intraluminal immune aggregates & subendothelial deposits that can be detected by light microscope	
5. Damage and tear GBM, plus glomeruli leucocyte infiltration	
B-tubulointerstitial changes	
Mononuclear cell infiltration	1. Interstitial fibrosis 2. Tubular atrophy

Drugs treatment

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 inhibitors (BARs). In addition, diet changes have an important effect on lowering blood pressure and controlling hyperlipidemia.

It is essential to avoid nephrotoxic agents such as nonsteroidal anti-inflammatory agents (NSAIDs) to limit further kidney injury. 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 (59), and the risk of abortion is high. Consequently, a woman should not conceive during SLE active status which requires these teratogenic agents. For a woman who insists on pregnancy, approaching close follow-up care and frequent kidney function tests are necessary (60). In addition, other associated systemic manifestations of SLE should be managed with agents that do not adversely affect the kidneys.

A. Immunomodulation drugs
Hydroxychloroquine (HCQ)

Some reported data indicate that HCQ enhances NT outcomes. HCQ reduces the risk of the tubulointerstitial inflammation (61), and complete response was noted during one HCQ treatment (62). LN progression to CKD and/or ESRD is significantly reduced with HCQ treatment. It was reported that removal of HCQ from the management plan of LN associates with 2 folds increase of death or ESRD or renal flare or requirement for rescue therapy during the LN management maintenance phase (63).

B. Immune suppressive therapy (table 1)
1.Corticosteroid

Steroids are utilized over a long period of time, they have proven an important long-term beneficial effect on their own, and especially in combination with other immunosuppressants such as cyclophosphamide. Nearly all patients with LN with active disease require a combined intravenous steroid and cyclophosphamide for inducing remission.

Although steroids are the mainstay of LN management, cyclophosphamide, azathioprine, mycophenolate, and other immune-suppressive drugs are sometimes added. In aggressive proliferative glomerulonephritis induced LN, aggressive combined therapy improves the renal outcome (64). Side effects of steroids such as osteoporosis should be sought and treated promptly by calcium, bisphosphonate, and vitamin D in some cases.

Minimum mesangial LN (Class I) does not require specific treatment, while Class II lupus nephritis may require treatment if proteinuria is greater than one gram/day. On the contrary, class III and IV patients are more likely to progress to ESRD, so they need aggressive treatment with immunosuppressive medications. Prednisone can be tried from 1 mg/kg/day for a minimum of 4 weeks and then gradually reduced based on clinical response. Most of these patients require 5-10mg/day of maintenance for approximately 2 years. Methylprednisolone intravenously at a maximum dose of 1000 mg/day for 3 days can be used in critically ill patients, followed by prednisolone orally. Patients who do not respond to corticosteroids alone and/or have unacceptable side effects to corticosteroids, adding others agents such as mycophenolate or azathioprine or others must be tried (3). Furthermore, patients have a worsening renal function, and/or have severe proliferative lesions, and/or evidence of sclerosis in renal biopsy specimens, a combination of steroid with another two immunosuppressive drugs are advisable (3). Long term use of high doses of steroids can cause weight increase, diabetes, hypertension, acne, facial swelling, edema, cushingoid appearance, psychosis, etc (3).

2.Azathioprine, Mycophenolate and Cyclophosphamide

Cyclophosphamide and azathioprine are equivalent, but cyclophosphamide is most effective in preventing ESRD following LN proliferation. Mycophenolate mofetil can be used on its own or sequentially after 6 months of IV treatment of

cyclophosphamide (65). Mycophenolate mofetil is less toxic and is effective as cyclophosphamide IV to prevent the progression of Class III and IV LN to ESRD (65).

Cyclophosphamide is typically given on monthly basis either as a single bolus or 2 divided doses for 6 months. Every 3 months reassessment of the clinical and laboratory responses is often done. Cyclophosphamide dose should be calculated according to renal function to reduce the risk of the side effects. Cyclophosphamide causes ovarian failure, therefore, gonadotropin-releasing hormone analog (leuprolide acetate) is given in females LN patients who are treated by cyclophosphamide, to prevent cyclophosphamide-induced ovarian failure (66).

Azathioprine can also be used as a second-line agent, although some nephrologists are using it as a first-line drug. It was reported that the response to mycophenolate mofetil was better than to azathioprine for LN relapse prevention in patients who had smooth induction therapy cycles (67). However, a 10-year follow-up of the MAINTAIN Nephritis Trial concluded that azathioprine and mycophenolate mofetil as maintenance therapy in proliferative LN gave an equal response (68). Although azathioprine and Mycophenolate may have the same effect in LN management, the follow-up, side effect, and cost must be considered (69).

Membranous LN (class V) patients are usually treated with prednisone for 1-3 months, then start tapering, then continue for 1-2 years if a response occurs. A study reported that azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, and chlorambucil are all effective in reducing proteinuria (70).

3.New agents under trial

Rituximab reduces B-lymphocytes count and activity (71). Rituximab was found effective in steroid resistance LN (72). A prospective observational single-center cohort study reported that the steroid-sparing regimen of rituximab and mycophenolate mofetil efficacy for LN was effective in maintenance therapy after one year (73). On the contrary, another study did not report a significant difference between rituximab and placebo, and rituximab effect was more effective in African American and Hispanic LN patients (74). Rituximab reduced serum anti-DNA antibodies and C3 and C4 level in active proliferative LN, although it did not change the clinical outcomes after 1 year of treatment (75).

Anti-CD20 monoclonal antibodies such as ofatumumab and ocrelizumab were tested in experimental studies in treating LN. The overall renal response was not statistically better than the placebo group (76).

Voclosporin (novel calcineurin inhibitor) plus mycophenolate mofetil and low-dose oral corticosteroids reported a partial response in the majority, and complete remission in about 30% of acute LN patients (77). It was reported that oral voclosporin effectiveness and safety were significantly higher with lower death rate, and proteinuria during one year treatment (78). Tacrolimus is another calcineurin inhibitor was reported effective in LN treatment, although most of the reported studies were form Asian patients, however, these agents were not thoroughly investigated for the long-term benefits and disadvantages (79).

Atacicept and Abetimus decrease the B lymphocytes and immunoglobulin levels in SLE patients (80). Abetimus is a B-lymphocyte tolerogen, and it is effective in preventing LN flares in a large, controlled trial, but it did not reduce the anti-DNA antibodies serum level (81).

Anticytokine therapies including monoclonal antibodies that are directed against Interferon-α, IL-1,6,10, and tumor necrosis factor-alpha (TNF-α) are preliminary effective in LN treatment, although further studies are needed (82).

Patients with stage V and VI lupus nephritis, as well as those who develop ESRD, global sclerosis, and a renal biopsy-based chronicity index, generally do not require aggressive immunotherapy. The best treatment modalities for these groups of patients include treating the extrarenal features of SLE and renal replacement therapy (RRT).

Table 2. Summary of clinical and laboratory features, treatment options, and prognosis concerning the classes of LN.

Class	Clinical & laboratory presentation	Treatment options	Prognosis
I	Asymptomatic, or Mild LL edema Normal renal function and GFR	No specific treatment	Excellent
II	Asymptomatic, or LL edema and may be mild high Bp Normal renal function, microscopic hematuria, or mild proteinuria If massive proteinuria, podocytopathy should be excluded	No specific treatment -Massive proteinuria: ACE or ARAB -Steroids and MMF or cyclophosphamide if steroid will be continued for 6months or more	Very good if Bp controlled and other SLE treatments are given
III	Red frothy urine, LL edema, and Bp may be increased Proteinuria and hematuria Some patients have features of nephrotic syndrome and deranged renal function, reduced GFR Marked reduction of GFR depends on the percentage of glomeruli affected. Features of class IV LN features occur	Steroids alone or in combination with cyclophosphamide or/and MMF	Usually, a good response and sustained remission occurs
IV	Red urine, LL edema, significant reduction of GFR, and/or high Bp Haematuria, Proteinuria +/- nephrotic syndrome range, increased urea and creatinine High anti-dsDNA titer and low serum C3, C4 Acute renal failure may occur	The same regime as for Class III	Usually, there is a good response, but relapse occurs, multiple cycles may be required
V	Change urine color, LL edema, high Bp Proteinuria +/- nephrotic syndrome, normal renal function, and microhematuria. Mild immunological activity changes	Steroid alone or with cyclosporine, MMF, or Azathioprine	Proteinuria improves, and progression to stage VI can be delayed
VI	High Bp, features of CKD	A. If chronic changes, no specific	ESRD

	Continuing GFR reduction with proteinuria and normal urinary sediment	treatment. B. If acute deterioration is going on, Trial of steroid plus one of the other immunosuppressive agents can be tried	

(BP: blood pressure; LL: lower limbs; MMF: mycophenolate; +/-: with or without; CKD: chronic kidney disease; ESRD: end-stage renal disease; LN: lupus nephritis)

Non-Pharmacological Management of ESRD in LN

1. RRT

In general, HD improves the clinical and serological disease activity as well as reduces the need for immunosuppression especially in black patients (83). HD is preferred over PD in LN induced ESRD. Several studies have documented that high dsDNA antibodies, thrombocytopenia, and higher steroid requirements are common among patients on PD. HD has an anti-inflammatory effect, and it reduces T-helper lymphocyte count (84). SLE flare-up is hidden and is not severe in hemodialyzed SLE patients, however, rash, arthritis, serositis, fever, and leukopenia occur, and need specific treatment, therefore, careful and frequent follow up are needed in these patients (85).

2. Renal transplantation

In the USA 3% of the transplanted patients are LN-induced ESRD patients. Before transplantation, it is essential to ensure that SLE is in remission status, and three months period of dialysis is usually advisable. It is well documented that the transplanted kidney in LN patients survives less than the kidney transplanted in patients without LN, and the patient outcome is better with living-related than the cadaveric allografts, although it can be conducted from cadaveric and non-related live donor with reasonable improvement of outcome (86). The reasons for the early graft failure in LN are not clear enough, however, they are probably due to LN reoccurrence and/or concomitant antiphospholipid antibody syndrome (87).

Conclusions

SLE is a multisystem disease, that may affect the kidneys, leading to unrecognized kidney involvement in one side of the scale and ESRD on the other side of the scale. The pathogenesis of the LN is not well explained; however, renal and extra-renal mechanisms have been postulated as contributors for LN pathogenesis. It seems that auto-immune mechanism(s) is/are the most probable cause, however, environment, diet habits, and other risk factors might be responsible for the pathogenesis and LN progression. Numerous treatment regimens have been proposed and tested with varying results that either support or discourage their use. RRT and renal transplantation are advisable in ESRD, however, further studies are needed to assess their effect on survival and outcome in LN. Besides, further studies are needed to explore the pathogenesis to develop effective strategies for the prevention and control of LN. LN management has improved in recent decades, but the critical need for consensual outcome measures remains to be analyzed and triaged.

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