Current and Emerging Therapy on Lupus Nephritis

Lucky A. Bawazier

Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta.

Corresponding Author:
Lucky Aziza Bawazier, MD., PhD. Division of Nephrology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia- Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: aziza.lucky17@gmail.com.

ABSTRAK

Nefritis lupus (NL) adalah keterlibatan organ ginjal pada pasien lupus eritematosus sistemik (LES) dan merupakan salah satu keterlibatan organ yang paling sering ditemukan. Ditemukannya NL pada pasien LES akan berdampak besar baik secara prognosis dari pasien maupun dalam pengobatan itu sendiri. Pengobatan NL dibagi menjadi dua tahap, induksi dan rumatan. Target dari pengobatan tahap induksi adalah untuk secepatnya mencapai remisi, baik parsial ataupun komplit, karena akan memberikan prognosis yang lebih baik dan kejadian relapse yang lebih rendah. Pada tahap rumatan, target yang ingin dicapai adalah untuk mempertahankan status remisi dan mencegah terjadinya relapse. Evaluasi keberhasilan dari masing-masing tahap juga sangat penting karena akan berpengaruh pada kelanjutan pengobatan. Kortikosteroid, siklofosfamid, mikofenolat mofetil, azatioprin, siklosporin dan takrolimus adalah obat-obat yang biasa dipakai dalam pengobatan NL. Berbagai target pengobatan baru juga terus berkembang guna memberikan pilihan yang lebih luas dalam menangani kejadian NL.

Kata kunci: *lupus eritematosus sistemik; nefritis lupus, ginjal.*

ABSTRACT

Lupus nephritis (LN) is involvement of the kidney in patient with systemic lupus erythematosus (SLE) and one of the most common target organ in SLE. The diagnosis of LN will significantly impact the clinical outcome and therapy of the patient. Therapy regiment of LN is divided into two stages, induction and maintenance treatment. The main objective of the induction therapy is to achieve complete or partial remission as soon as possible since it is correlated with better prognosis and fewer relapse incidence. In the maintenance stage, the main aim of the therapy is to maintain the remission status and avoid future relapse. It is also important to evaluate the effectiveness of the therapy as it will affect the duration and the regiment therapy being used. Corticosteroid, cyclophosphamide, mycophenolate mofetil, azathrioprine, cyclosporine and tacrolimus are example of drugs used in LN therapy. Currently, studies are being conducted to evaluate and develop targeted drug therapy to further add treatment options for LN.

Keywords: *systemic lupus erythematosus; lupus nephritis; kidney.*

INTRODUCTION

Renal involvement in systemic lupus erythematosus (SLE) plays a major factor that impact the clinical outcome on the patient. Lupus nephritis (LN) was found in 40 – 60% of SLE patients and can increase up to 70% over 10-year period after initial diagnosis.[1] Recent data shows 10-year survival of LN patient to range between 77 to 95%.[2] Despite advances in treatment, 26% of LN patients still develop end-stage renal disease (ESRD) which cause a reduced in life expectancy by 15.1 – 23.7 years. Infections, cardiovascular complication and malignancy contribute to the main cause of death associated with long-term LN treatment.[3] The review aims to compare the regiments in terms of efficacy and safety for better clinical practice outcome.

CURRENT INDUCTION THERAPY

Induction therapy is pivotal in treating patients with lupus nephritis (LN), the goal is to minimize renal damage, achieve rapid remission and/or complete remission.[4] An effective induction therapy has been proven to give fewer episodes of relapse and better prognosis.[4]

Induction therapy for LN patients is a continuously studied topic.[4-6] In 1986, National Institutes of Health reported its 10-year follow up research and found that by combining high-dose steroids and cyclosphophamide (CYC) it gave a significantly better 10-year renal survival result than steroids alone.[7] However, CYC also resulted various side effects such as suppression of bone marrow, malignancy, opportunistic infection, and so forth.[7] Despite, administration of steroids combined with intravenous (IV) CYC became the gold standard in treating LN patients until present.[6]

Since then, researchers look for a safer immunosuppressants agents to replace CYC, for example mycophenolate mofetil (MMF), azathrioprine (AZA), cyclosporine, and tacrolimus. MMF is the most promising alternative for CYC, although results from literatures displayed various results in inducing remission of LN between the two immunosuppressant's agents.[4,6,8] Some studies concluded that MMF is more superior than CYC.[9-11] On the other hand, others found that MMF is not-inferior or equal to CYC.[12,13] Nevertheless, most clinicians favor the use of MMF. Unfortunately it is not covered in the health insurance program in Indonesia.[5]

Currently, researchers focus on multitarget induction therapy; combining multiple drugs to achieve better results and fewer side effects and shows promising results.[14,15] A study in China compared a combination of tacrolimus, MMF, and steorids with the traditional IV CYC and steroids.[13,14] The multitarget regiments showed a higher incidence of complete remission and less adverse events. A retrospective analysis in Japan was conducted to examine the efficacy and safety of multitarget induction therapy using tacrolimus, MMF, and steroid with comparison of TAC Therapy (tacrolimus and steroid).[15] It was found that all patients treated with multitarget therapy had complete remissions. A meta-analysis of randomized trials was done in 2017 to compare the efficacy and toxicity of newer immunosuppressants for LN.[16] The study compared IV CYC, oral CYC, MMF, calcineurin inhibitor (CNI), plasma exchange, rituximab, or azathioprine, alone or in combination. The study stated that MMF combined with CNI was the most effective treatment to induce remission, followed by CNI alone and MMF alone.[16] Although, it was also found that there was no difference on end-stage kidney disease or increasing of serum creatinine level between MMF or CCI (alone or in combination) and IV CYC.

According to Kidney Disease Improving Global Outcomes (KDIGO) 2012, the use of immunosuppressants are indicated for Class III/IV LN.[17] Class V LN are also given immunosuppressants in regards that endocapillary hypercellularity and/or subendothelial immune deposits is present and persistent nephrotic proteinuria.[17] **Figure 1** shows the algorithm of induction therapy for LN.

As for Class I LN, KDIGO 2012 does not recommend treatment due to no available data to suggest that it needs therapy.[17] However, Class II LN with proteinuria under 1 g/d should be treated for extrarenal clinical manifestations and Class II LN with uncontrolled proteinuria (over 3 g/d) should be treated with corticosteroids or CNIs.[17]

KDIGO 2012 recommended 4 regiments to

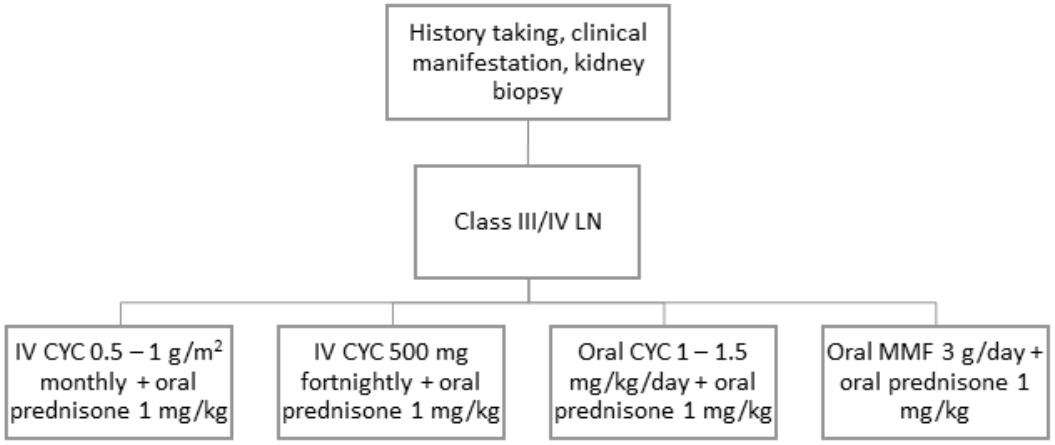

Figure 1. Induction therapy algorithm according to KDIGO 2012.[17]
(LN = lupus nephritis; IV CYC = intravenous cyclosphophamide; CYC = cyclosphophamide; MMF = mycophenolate mofetil)

be used in induction therapy, which are: Regimen A (NIH regimen), Regimen B (Euro-Lupus regimen), Regimen C (oral cyclosphophamide), and Regimen D (MMF).[17] All regimens used the same steroid dosing: initial dose of oral prednisone 1 mg/kg, tapering according to clinical response over 6-12 months. Dosage and duration of the regimens can be seen in **Table 1**. In addition, according to the Spanish Society of Nephrology (SEN) and Society of Internal Medicine (SEMI) dosage of Regimen B has minimum risk, almost to none, of ovarian failure because the total CYC given does not exceed 10 g.[18]

Table 1. Regimens for induction therapy in class III/IV LN according to KDIGO 2012[17]

Regimen	Dosage	Duration
NIH	IV CYC 0.5-1 g/m^2 monthly	6 months
Euro-Lupus	IV CYC 500 mg fortnightly	3 months
Oral Cyclosphophamide	Oral CYC 1-1.5 mg/kg/day	2-4 months
MMF	Oral MMF 3 g/day	6 months

If the patients have worsening LN or flare during the first 3 months, alternative induction therapy can be used as a replacement.[17] **Table 2** shows the immunosuppressants used in LN.

Class VI LN is described as chronic injury, where over 90% of the glomeruli are sclerotic.[17] KDIGO 2012 does not recommend immunosuppressive therapy for this class, nevertheless, patients with extrarenal manifestations must be treated with immunosuppression agents.[17]

Table 2. Immunosuppressants used in LN[17]

Immunosuppressant Agents	Dosage
CYC	IV 0.5-1 g/m2; Oral 1-1.5 mg/kg/day
MMF	3 g/day
AZA	-
Cyclosporine	4-5 mg/kg/day
Tacrolimus	4 mg/day*

CYC = cyclosphophamide; IV = intravenous; MMF = mycophenolate mofetil; AZA = azathioprine; * = combined with MMF 1 g/day

American College of Rheumatology (ACR) also made a guideline for therapy of LN. MMF 2-3 g daily or IV CYC along with IV pulse steroids (500-1000 mg methylprednisolone daily for 3 doses) for Class III/IV LN are the recommended regimens, and both are considered equivalent based on recent studies.[19] There are 2 recommended dosage for IV CYC, which are: low-dose CYC (500 mg IV fortnightly for a total of 6 doses) followed by maintenance therapy with daily oral AZA and high-dose CYC (500-1000 mg/m^2 IV monthly for 6 doses) followed by maintenance therapy with MMF or AZA.[19] **Figure 2** shows the algorithm made by ACR.

Class V LN have different recommendation than Class III/IV LN according to ACR. They recommend the administration of prednisone (0.5 mg/kg/day) combined with MMF 2-3 g total

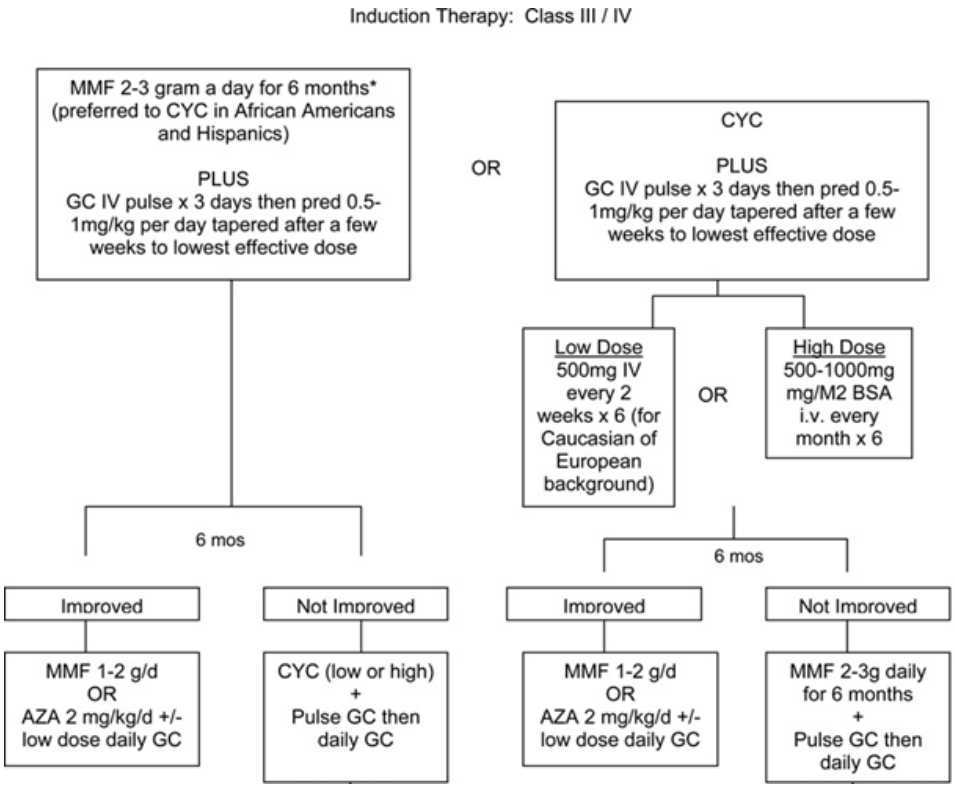

Figure 2. Induction therapy for LN according to ACR.[19]
(MMF = mycophenolate mofetil; CYC = cyclosphophamide; GC = glucocorticoids; IV = intravenous; AZA = azathioprine; BSA = body surface area)

daily dose.[19]

If an adequate respond to induction therapy is not achieved, ACR recommend that a switch of the immunosuppressants from either CYC to MMF or from MMF to CYC accompanied by IV pulse steroids for 3 days.[19]

According to ACR, Class I and Class II LN does not require immunosuppressive therapy.[19] Furthermore, hydroxychloroquine (HCQ) must be given to all systemic lupus erythematosus (SLE) patients with nephritis as it has been proven to lower renal damage and reduce the risk of clotting events.[19] In addition, LN patients with proteinuria over 0.5 g/d should be given renin-angiotensin system (RAS) blockers such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).[19] As for Class VI LN, it requires renal replacement therapy rather than immunosuppressive therapy.[19]

CURRENT MAINTENANCE THERAPY

The target of induction therapy in treating lupus nephritis (LN) is to rapidly attenuate inflammation process caused by accumulation of autoantibody immune complex and to give chance to parenchymal tissue for healing process.[20] After this phase of treatment, only few patients achieve complete clinical remission, as renal response rates showed 50-80% at 1 year with the majority of the response was partial response.[21] In order to consolidate remissions and prevent relapses of LN, one must receive maintenance therapy.

Guidelines of lupus nephritis treatment still recommends the use of either MMF or AZA as the choice of maintenance therapy. There was still no definitive first line choice between the two options. Based on KDIGO (2012), in making the decision of treatment choice, clinical adjustments such as pregnancy plan or occurrence of side effects are considered.[22] The use of AZA as maintenance therapy is preferred if patient plan for pregnancy.[23] Treatment guidelines by ACR (2012) recommends the use of either mycophenolate mofetil (MMF) 1-2 g/day or azathiprone (AZA) 2 mg/kg/day in maintenance therapy of LN.[19]

There were two big clinical trials aiming for optimal maintenance therapy for LN, which were the MAINTAIN study and Aspreva Lupus Management Study (ALMS). These two studies compared effectiveness between MMF and AZA.

In ALMS trial, 227 patients were randomized to receive either MMF (2 g/day) or AZA (2 mg/kg/day). The follow-up duration was 36 months. The primary end point was time to treatment failure (death, end-stage renal disease, doubling of serum creatinine level, renal flare, or rescue therapy). This trial showed that MMF was superior to AZA in the aspect of time to treatment failure (hazard ratio 0.44; 95% confidence interval, 0.25—0.77; P=0.003) and time to rescure therapy (hazard ratio <1.00; P<0.05). Serious adverse events occurred more in AZA group than in MMF group (33.3% vs 23.5%, P=0.11).[24]

In MAINTAIN trial, with the same follow up duration (36 months), 105 patients were randomized to receive either MMF or AZA with the same dosage.[25] Time to renal flare in MMF and AZA group were statistically insignificant (19% and 25% respectively).[25]

The duration of therapy in maintenance phase is still questionable. According to KDIGO 2012, the average duration of maintenance therapy was 3.5 years.[22] A guideline by Spanish Society of Nephrology (GEAS) recommended that duration of maintenance therapy was 2 years after complete remission.[26] Euro-Lupus Nephritis trial was a ten-year follow-up study which showed that 53% of the patients were still on maintenance therapy. Advice from the Dutch's guideline on LN stated that clinicians should taper the dose of prednisone to 10 mg every other day at four years after the beginning of induction therapy and followed by decreasing 50% dose of AZA or MMF 6 months later and continue until at least two more years.[27] After 6.5 years, it is left to the treating clinician's decision and the patient's.[28] **Table 3** summarize the comparison of guidelines on the maintenance therapy of lupus nephritis class III/IV.

EVALUATION

Currently, the gold standard of care for patients with lupus nephritis (LN) after induction therapy is to administer maintenance therapy for around 3 years. In a subset of patients with clinically silent disease, the decision to stop maintenance therapy should be done with caution. In order to decide whether these patients

Table 3. Comparison of guidelines on maintenance therapy of lupus nephritis class III/IV

Guidelines	Corticosteroid	Immunosuppresive Agent Choice	Duration and Dosage Tapering
Kidney Disease Improving Global Outcomes (KDIGO)[22]; 2012	Low-dose oral corticosteroids (≤10 mg/day prednisone equivalent)	MMF 1-2 g/day or AZA 1.5-2.5 mg/day	Continue at least 1 year after complete remission
European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA)[23]; 2012	Low-dose oral corticosteroids	MMF or AZA. MMF was preferred if there was adequate response to MMF in induction phase.	Three years after complete remission.
American College of Rheumatology (ACR)[19]; 2012	Low-dose oral corticosteroids	MMF 1-2 g/day or AZA 2 mg/kg/day	Not specified. The Task Force Panel did not vote on the rate of medication taper in maintenance phase.
Systemic Autoimmune Disease Group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology (GEAS)[26]	Low-dose oral corticosteroids	MMF over AZA	Two years after complete remission.
Dutch Guidelines for Diagnosis and Therapy of Proliferative Lupus Nephritis[28]; 2012	Low-dose oral corticosteroids	MMF over AZA	Taper prednisone 10 mg every other day at 4 years after the beginning of induction phase, decrease 50% dose of AZA or MMF after 6 months, and continue at least 2 more years (Total: 6.5 years)

do not need further therapy, repeated renal biopsy to confirm the histological evidence of non-active LN and laboratory work needs to be performed. Repeat kidney biopsy in patients who have completed and responded well to the maintenance course treatment can also be planned to decide whether the therapy should be discontinued.[29] The reason to be cautious before stopping therapy is that LN could still be active after several years of immunosuppressive therapy. Renal flares after treatment withdrawal could lead to a more progressive chronic kidney injury. There are several criteria available to assess the renal response after therapy. However, those criteria are based on serum creatinine level, estimated glomerular filtration rate (eGFR), proteinuria, urine protein creatinine ratio (UPCR), hematuria, urinary sediment and cast. Furthermore, flare criteria definition has been based on a guideline by KDIGO which has criteria similar as to check renal response to therapy.[30] **Table 4** presents the relapse renal flare criteria based on KDIGD guidelines.

NOVEL AND EMERGING TREATMENT OF LUPUS NEPHRITIS

The pathogenesis of lupus nephritis (LN) is associated with activation of mainly B and T cells. Activation of B cell further leads to formation of plasma cells and subsequently autoimmunity against the kidney, which will induce kidney damage through inflammation process. On the other hand, antigen presenting cells falsely presents autoantigen unto T cells which induces further inflammatory process through activation of pro-inflammatory cytokines. Various pro-inflammatory cytokines have been described to be implicated in the pathogenesis of LN but it seems that interferon-α (IFN-α) is the master regulator of stimulating the differentiation of B cells and T cells.[31,32] As stated before, B cells play an important role in LN and therefore it is an attractive target in LN treatment. One example of popular B cell depleting agent is rituximab, an anti-CD20 monoclonal antibody which has been studied extensively with mixed results. Several early studies have reported potential benefit of rituximab. However, Lupus Nephritis Assessment with Rituximab Study (LUNAR) failed to reproduce the same results from previous studies.[33]

Currently, there is still ongoing interest in studying the effect of rituximab and other B cell depleting agents in the treatment of LN. Scientists have questioned the trial design of LUNAR study as it was rather a short-term rather than a long-term study. Rituximab as a B cell depleting agent has been argued not to resolve

Table 4. Relapse/renal flare criteria based on KDIGO guideline[22]

Mild Relapse	Moderate Relapse	Severe Relapse
Increased of hematuria from <5 to >15 erythrocyte/HPF, with >2 acanthocyte/HPF	If baseline serum creatinine (sCr) <2 mg/dL, moderate relapse is defined as increased of sCr 0.2-1 mg/dL	If baseline creatinine <2 mg/dL, severe relapse is defined as increased of sCr >1 mg/dL.
With/without	If baseline serum creatinine (sCr) >2 mg/dL, moderate relapse is defined as increased of sCr 0.4-1.5 mg/dL	If baseline creatinine >2 mg/dL, severe relapse is defined as increased of sCr >1.5 mg/dL.
Recurrence of >1 erythrocyte, leucocyte (without infection), or both	With/without	With/without
	If baseline urine protein creatinine ratio (uPCR) <500 mg/g, moderate relapse is defined as increased of uPCR >1000 mg/g.	Increased of uPCR >5000 mg/g
	If baseline uPCR 500-1000 mg/g, moderate relapse is defined as increased of uPCR between 2000-5000 mg/g.	
	If baseline uPCR >1000 mg/g, moderate relapse is defined as increased of uPCR >2 times with absolute uPCR <5000 mg/g.	

acute inflammation of the kidney, but rather it might prevent future renal flares since it works by inhibiting autoimmunity response and not the acute inflammation process.[37] To address this concern, a trial is underway to investigate the effect of similar B cell depleting agent like rituximab, which involves obinutuzumab, a type-2 chimeric, anti-CD20 monoclonal antibody. Early initial studies reported better results than rituximab. Therefore, it is currently in clinical trial to evaluate the depletion of B cells in kidney tissues.[38.39]

Another example of potential B cell depleting agents are belimumab and tabalumab, an anti-BAFF monoclonal antibody. B cells activating factors (BAFF) is needed to induce B cell proliferation and survival, thus the use of this agent in LN treatment is promising.[40] Current topic suggests that BAFF level increases after B cell depletion. It is stated that reactivation of B cells in BAFF-rich environment after B cells depletion will lead to more autoreactive B cells, which bypass the tolerance checkpoints. It is known that high BAFF level is associated with renal flares in SLE. Hence, it is suggested that targeting BAFF after initial B cell depletion is essential to prevent reactivation of B cells and hopefully make these B cells more tolerant, less autoreactive, and more sustained clinical response. The immune tolerance network CALIBRATE study is currently testing this hypothesis in clinical trial.[41]

Plasma cells are also an interesting target in SLE. It is a product of B cell activation which produces autoimmunity against self-antigen. Even though B cell depleting agents have been widely used, those agents do not directly eliminate all plasma cells which have been formed before the therapy is given.[42] Plasma cells, especially the long-lived one, can produce autoantibody and have been found in SLE during flare. Current standard treatment does not target the plasma cells in order to supress the long-lived plasma cells, but rather it emphasizes more on B cells depletion.[43] Proteasome inhibitor targets the plasma cells and induces apoptosis. Several example of its agents are bortezomib, carfilzomib, delanzomib, and ixazomib. Proteasome inhibitor is also known to have dual mechanism of action as anti-inflammatory by suppresing IFN-α and as anti-autoimmunity. Currently, there are several clinical trials evaluating patients who are not responsive to initial standard of care treatment.[44]

IFN-α is a key biological target to attenuate inflammatory process in SLE and LN patients. An example of an IFN-α which is currently in clinical trial is Anifrolumab, a monoclonal antibody that targets IFN-α receptor 1. Anifrolumab has shown its efficacy in non-renal SLE when compared to placebo in patients who have high type IFN-α signature. The TULIP LN 1 study is undergoing an investigation of anifrolumab combined with the gold standard treatment for proliferative LN. In this study, the researchers divides patients into

Table 5. Response criteria definitions

Study	Complete Remission	Partial Remission
National Institute of Health (NIH)[34]	SCr <130% from the lowest value, proteinuria <1 gr/24 hour, hematuria <10 red blood cells/HPF, without evidence of cellular cast	SCr <150% from the lowest value
Euro-lupus Nephritis Trial (ELNT)[35]	This guideline does not divide remission criteria into complete or partial. Remission criterias are as follow: Hematuria <10 red blood cell/HPF, proteinuria <1 gr/24 hour, sCr value does not increase 2 times above normal value.	
American College of Rheumatology (ACR)[19]	50% decrease of uPCR + uPCR <0.2	50% decrease of uPCR + uPCR 0.2-2.0
KDIGO[36]	SCr returns to baseline, plus decrease of uPCR <500 mg/gr (<50 mg/mmol).	Stabilized (±25%) or improvement of SCr but not return to normal, plus decrease of uPCR >50%. If nephrotic proteinuria is found, uPCR should decrease >50%.

two groups. The first group consists of patients who have high IFN-α and the other group who have low IFN-α concentration. This is necessary to prevent treating patients who do not actually express the drug's target which predictably will result in treatment failure.[45]

Another appealing therapy strategy in LN is to target complement pathway. This alternative pathway seems to be important to cause kidney damage through inflammation process.[46] Current example of complement activation products include C3bi, C5a, and C5b-9. There is a hypothesis stating that inclusion of complement targeted therapy in combination with gold standard treatment might help to attenuate inflammation and reduce the use of corticosteroid.[47] However, evidence of its efficacy in LN has not been extensively evaluated. Therefore, further research regarding agents which target this pathway is important.[48]

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