Assessment and Management of treatment resistant Lupus Nephritis

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Contents

Assessment of Treatment Response

- Assess response 3-4 months after initial therapy
- clinical response (reduced proteinuria, stabilized serum creatinine, improved urinary sediment).
- True resistance is rare, often due to non-adherence or treatment difficulties.
- No consensus on complete response definition with immunosuppressive treatment in proliferative LN, leading to variable refractory LN incidence.

Overview of EULAR/ERA-EDTA Guidelines for Lupus Nephritis

Refractory Lupus Nephritis

failure to achieve a partial response after 6–12 months(reduction in proteinuria > 50% to a non nephrotic range)

complete response after 2 years of treatment(inactive urinary sediment, decreased proteinuria to <0.5 g/day and normal or stable creatinine)

Management of Treatment Resistance

- Adherence Verification

First step in management is to assess and ensure patient adherence to the initial therapy

- Nonadherence Causes

Factors like medication side effects, socioeconomic status, health literacy, and access can affect adherence

- Approach to Nonadherence

Use nonjudgmental questions, measure drug levels, and tailor approaches like switching therapies or using reminders and organizers.

Understanding Non-Adherence Prevalence in Lupus Nephritis

- Prevalence Rate:approximately 30-50%
- In an analysis of 13,429 Medicaid beneficiaries with SLE who were new users of hydroxychloroquine or immunosuppressive medications, 79 percent of new users of hydrochloroquine and 83 percent of new users of immunosuppressive medications were nonadherent to therapy

Costedoat-Chalumeau N, Houssiau FA. Improving medication adherence in patients with lupus nephritis. Kidney Int 2021; 99:285.

Strategies to Address Patient Non-Adherence

- Identify Beliefs and Barriers

Start by discussing the patient's beliefs about their medication. For example, if a patient thinks their medicine isn’t working or fears side effects, understanding these thoughts helps tailor solutions. Listening openly can reveal barriers like daily routines that make remembering to take medications more challenging.

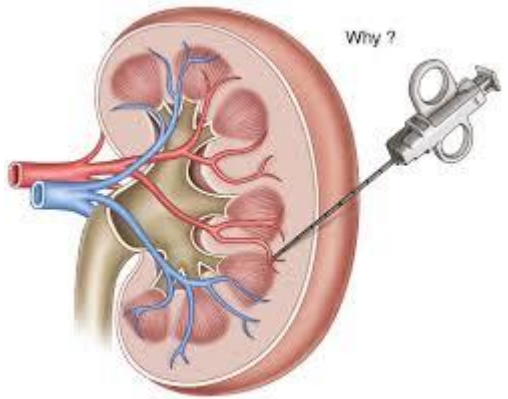
Strategies to Address Patient Non-Adherence

- Simplify Medication Regimens

Consider simplifying the medication schedule. For instance, instead of three daily doses, switching to a once-daily pill can significantly improve adherence. Using pill organizers or setting reminders on smartphones are great tools. Don't hesitate to ask patients for feedback on what would work best for them!

When Repeat Kidney Biopsy?

In cases of focal or diffuse LN not responsive to initial therapy, consider a repeat kidney biopsy to differentiate between active inflammation and chronic changes, or to exclude an alternative diagnosis before changing immunosuppressive therapy



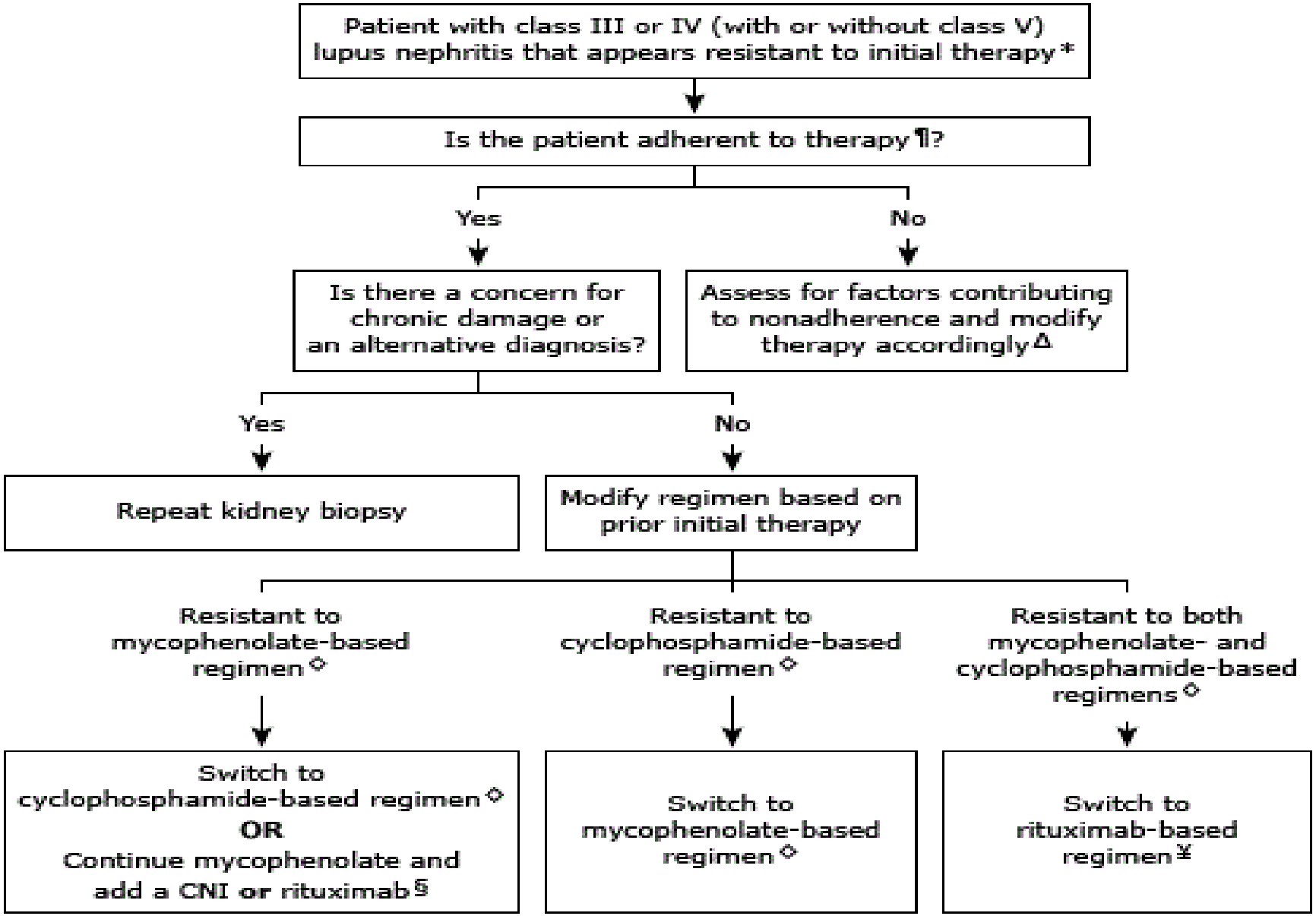
Feldman CH, Yazdany J, Guan H, et al. Medication Nonadherence Is Associated With Increased Subsequent Acute Care Utilization Among Medicaid Beneficiaries With Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken) 2015; 67:1712

Specific Management Strategies

Based on prior initial therapy:

1. Patients Resistant to MMF: Switch to intravenous cyclophosphamide plus glucocorticoids, or consider adding CNI or rituximab to MMF.
2. Patients Resistant to Cyclophosphamide: Switch to MMF plus glucocorticoids, or consider combination with CNI, belimumab, or rituximab.
3. Patients Resistant to Both Treatments: Use rituximab-based regimens; no randomized trial data, but observational studies suggest possible benefit.

Anders HJ, Lei Y, Rovin BH. Induction and maintenance therapy of lupus nephritis: an obituary. Kidney Int 2021; 99:288


Patient with class III or IV (with or without class V) lupus nephritis that appears resistant to initial therapy*
Is the patient adherent to therapy¶?
Yes
No
Is there a concern for chronic damage or an alternative diagnosis?
Assess for factors contributing to nonadherence and modify therapy accordingly Δ
Yes
No
Repeat kidney biopsy
Modify regimen based on prior initial therapy
Resistant to mycophenolate-based regimen ◇
Resistant to cyclophosphamide-based regimen ◇
Resistant to both mycophenolate- and cyclophosphamide-based regimens ◇
Switch to cyclophosphamide-based regimen ◇ OR Continue mycophenolate and add a CNI or rituximab §
Switch to mycophenolate-based regimen ◇
Switch to rituximab-based regimen ¥

- There is limited evidence to suggest that combination therapy with MMF is effective among MMF-resistant patients. In one observational study, tacrolimus (0.075 mg/kg/day) was added to MMF in 17 patients with MMF-resistant class IV (n = 15) or class V (n= 2) LN [17]. After a mean follow-up of 24 months, six patients (35 percent) had a complete response (defined as urinary protein excretion of <0.3 g/day, normal sediment, and normal or stable kidney function), and six patients had a partial response (defined as protein excretion of <2.9 g/day with stable or improved kidney function). Tacrolimus was well tolerated.

Choi CB, Won S, Bae SC. Outcomes of multitarget therapy using mycophenolate mofetil and tacrolimus for refractory or relapsing lupus nephritis. Lupus 2018; 27:1007

- Limited data from small case series suggest that MMF may be effective in treating patients who are resistant to cyclophosphamide. As an example, in one series of 12 patients who were resistant to or relapsed following cyclophosphamide and treated with MMF for a mean of 13 months, proteinuria decreased and serum creatinine was stable or decreased in 10 patients.

Weidenbusch M, Römmele C, Schröttle A, Anders HJ. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant 2013

- The choice among these regimens depends upon several factors, including clinician and patient preference, drug availability and cost, toxicity, and tolerability.

- There is no evidence directly comparing these regimens in the treatment of patients with resistant focal or diffuse LN, and this approach is largely based upon our clinical experience and expert opinion.

- The largest reported experience included 23 patients with focal or diffuse LN who had persistent disease activity despite a variety of immunosuppressive drugs; most had been treated with cyclophosphamide (11 patients) or MMF (12 patients) as well as other drugs (eg, cyclosporine, azathioprine).Rituximab (0.5 to 1 g on days 1 and 15) was added to the existing immunosuppressive regimen. Three months after the administration of rituximab, five patients had a complete response (normal serum creatinine, inactive urine sediment, and protein excretion of 40 percent improvement in kidney parameters).

Davies RJ, Sangle SR, Jordan NP, et al. Rituximab in the treatment of resistant lupus nephritis: therapy failure in rapidly progressive crescentic lupus nephritis. Lupus 2013; 22:574

Plasma exchange and immunoadsorption

- The evidence for extracorporeal treatments such as plasma exchange and immunoadsorption in refractory LN is minimal, based mainly on single case reports and observational studies.
- A randomized, controlled trial conducted by the Lupus Nephritis Collaborative Study Group examining the efficacy of plasma exchange when added to standard therapy in patients with severe LN failed to show improvement in clinical outcomes.
- In a study of eight patients with refractory disease who underwent immunoadsorption and had concomitant CYC, all patients had reductions in creatinine and urinary protein excretion.
- Extracorporeal therapies have sometimes been considered for patients with contraindications to standard therapy including severe infection risk and significant leucopenia as well as other indications such as pulmonary hemorrhage

Soyuöz A, Ö K, Karaağaç T, Kılıç L, Ş A B, Özcebe O. Therapeutic plasma exchange for refractory SLE: a comparison of outcomes between different sub-phenotypes. Eur J Rheumatol. 2018;5 (1):32–36. doi:10.5152/eurjrheum.2017

Investigational biologic therapies

- Access to such agents are limited to trials at this stage
- B cell survival factors; B lymphocyte stimulator (BLyS) and a proliferation inducing ligand (APRIL) are key survival cytokines for B cell survival and development. They bind to three different receptors: transmembrane activator and calcium-modulating cytophilin ligand interactor (TACI), the B cell maturation antigen (BCMA) and the BAFF receptor (BAFF-R).Overexpression of BLyS promotes survival of B cells (including autoreactive B cells), whereas inhibition of BLyS results in autoreactive B cell apoptosis. Elevated circulating BLyS and APRIL levels are seen in SLE and correlate with increased SLE disease activity and elevated anti-double stranded DNA (anti-dsDNA) antibody concentrations.

Merrill JT, Wallace DJ, Wax S, et al. Efficacy and safety of atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. Arthritis Rheumatol. 2018

Belimumab

- Belimumab is the first new drug approved by both the FDA and by the European Medicines Agency for antibody-positive SLE in decades. Belimumab is a human monoclonal IgG1 antibody that binds to and inhibits soluble B-lymphocyte stimulator protein. It was found to be superior compared with placebo
- Although patients with severe LN were excluded from this study, a pooled post-hoc analysis of the cohort indicated that over 52 weeks there was a significant reduction in the frequency of renal flares and a tendency for greater reduction in proteinuria. A phase 3 randomized controlled trial is currently underway to evaluate the efficacy of belimumab in LN.

. Mosanya CH, Isaacs JD. Tolerising cellular therapies: what is their promise for autoimmune disease? Ann Rheum Dis. 2018

Co-stimulation blockade

- Abatacept is a soluble Fc CTLA-4 fusion protein that prevents T cell activation by competing with CD28 for binding to CD80-86, a costimulatory signal required for T cell activation. Evidence from the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) trial, failed to demonstrate any benefit of abatacept plus low dose CYC compared to placebo plus low dose CYC.
- Interestingly, patients on the abatacept arm who reached complete renal remission at 6 months were followed for another 6 months without any maintenance immunosuppressive therapy.
- At 12 months, the patients in the abatacept arm had fewer renal flares.
- Recently completed, the largest randomized controlled trial in LN had 405 participants and sought to compare abatacept to placebo when added to standard of care therapy consisting of mycophenolate and steroids. Disappointingly, there was no difference in the primary end point of complete renal remission at week 52 (abatacept 35% and placebo 33%, p=0.73).

. Mosanya CH, Isaacs JD. Tolerising cellular therapies: what is their promise for autoimmune disease? Ann Rheum Dis. 2018:

Epratuzumab

- Epratuzumab is a humanized monoclonal antibody of the IgG1 class that targets CD22 on B cells, disrupting the B cell receptor signaling complex and resulting in modulation of B cell activity without substantial reductions in the number of peripheral B cells. The EMBODY 1 and EMBODY 2 phase III multicenter randomized placebo-controlled double blinded trial was conducted in patients with moderately to severely active SLE, though excluded patients with LN. Treatment with epratuzumab in conjunction with standard therapy did not result in improved outcomes at week 48 when compared to placebo. Phase III trials in LN have yet to be conducted.

Costedoat-Chalumeau N, Houssiau FA. Improving medication adherence in patients with lupus nephritis. Kidney Int 2021; 99:285

Atacicept

- Atacicept is a recombinant fusion protein comprising the extracellular domain of the TACI receptor joined to a human IgG1 Fc domain. Atacicept blocks B cell stimulation by both BLyS and APRIL pathways. In 306 patients with active, autoantibody positive non-renal SLE receiving standard of care, there was a trend towards efficacy when compared to placebo.

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Anifrolumab

- Interferon-alpha appears to have a central regulatory role in SLE and LN and is therefore a potential treatment target. Recent phase III clinical trial, the TULIP-1 study, examined the efficacy of anifrolumab, a monoclonal antibody against IFN-alpha receptor 1, versus placebo in patients with moderately-severely active auto-antibodypositive non-LN SLE and, failed to meet the primary endpoint of a reduction of disease activity as measured by the SLE Responder Index .The TULIP-2 trial and TULIP-LN1 trial, examining the efficacy of anifrolumab in active proliferative LN, is ongoing

Mesenchymal stem cell transplantation

- In some studies, allogeneic mesenchymal stem cell (MSC) transplantation has been used with good results. MSCs have immunomodulatory functions, including their ability to stimulate the differentiation and proliferation of regulatory T cells. In one study, MSC transplantation was performed in 15 patients with refractory LN. After 12 months of follow-up, the proteinuria decreased from 2505mg/day to 858mg/day. There were no life-threatening side effects after the procedure, unlike what happens in autologous stem cell transplant.
- In a follow-up study of the same group, a remission rate of 60.5% and a relapse rate of 22.4% were established.

.Mosanya CH, Isaacs JD. Tolerising cellular therapies: what is their promise for autoimmune disease? Ann Rheum Dis. 2018:

THANK YOU FOR YOUR ATTENTION