Position Statement and Consensus Recommendation of the Immunonephrology Working Group of the Portuguese Society of Nephrology on the Management of Proliferative Lupus Nephritis and the Use of Old and Emergent Combination Therapies

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Abstract
lupus nephritis is an immune complex mediated glomerulonephritis representing one of the most severe manifestations of systemic lupus erythematosus. Despite advances in therapy, progression to chronic kidney disease remains significantly high, underlining the need for more effective drug regimens that encompass less long-term toxicity.
Recently, lupus nephritis has been reframed as a form of chronic kidney disease, shifting therapeutic goals toward three main pillars: sustained immunological control with prevention of relapse, interventions that target non-immune factors of chronic kidney disease and strategies that minimize infection risk.
The emergence of novel therapeutic agents has prompted updates of major international guidelines, with new combination drug schemes that increase efficacy and allow glucocorticoid sparing. This position statement reviews the KDIGO 2024, ACR 2024, and EULAR 2025 recommendations and presents the Immunonephrology Working Group of the Portuguese Society of Nephrology perspective on the management of proliferative Lupus nephritis – Classes III and IV, according to our national context.

Keywords: Immunosuppressive Agents/therapeutic use; Lupus Erythematosus, Systemic; Lupus Nephritis; Practice Guideline

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic and complex immune mediated disease that frequently involves the kidney. Renal immune complex mediated inflammation and tissue damage designated as lupus nephritis (LN) can occur at any time during SLE course in 30% to 70% of patients, depending on their geographic origin and ethnicity.[1,2] The introduction of cyclophosphamide (CYC) markedly reduced the progression of lupus nephritis (LN) to end-stage renal disease (ESRD). However, studies have shown that in the last 20 years, ESRD has reached a plateau, meaning that new and more effective drugs are needed to improve LN long-term outcomes.[3-5] In Portugal, a multicenter national study of 260 LN patients, revealed that only 62% reached renal remission at one year.[4] Improving complete renal remission (CRR) rates and reducing ESRD incidence, while minimizing treatment -related toxicity, particularly from high-dose glucocorticoids (GC), remain key unmet needs in LN therapy.

Over the past years, the perspective of LN global therapy changed and is now also being approached as an important cause of chronic kidney disease (CKD). As such, LN treatment should now focus on drugs and strategies that minimize immunological LN activity and prevent relapse (including subclinical activity), interventions that target non-immune factors of CKD (including physical exercise, reduction of cardiovascular risk, and drugs that slow CKD progression and on measures that reduce the risk of infection (such as lowering GC dose and vaccination).[6]

The emergence of new drugs and their incorporation in combined LN regimens occurred in the last years, driving the need for an update of LN guidelines. In this position statement, the Immunonephrology Working Group of the Portuguese Society of Nephrology (INWG) will review the LN Kidney Disease Improving Global Outcome (KDIGO) 2024, American College of Rheumatology (ACR) 2024 and European Alliance of Associations for Rheumatology (EULAR) 2025 guidelines[7-9] and will expose its view on the management of proliferative LN, considering our national context.

METHODS

This position statement was developed by the INWG with the aim of providing pragmatic recommendations for the management of proliferative LN in adult patients within the Portuguese healthcare system. The document integrates recent international guideline updates with trial data and national expert opinion.

Scope and guiding questions

The Working Group first defined the scope of the document and key clinical questions, focusing on: (i) initial and subsequent immunosuppressive treatment of proliferative LN; (ii) the role of combination and socalled “triple” regimens; (iii) strategies for GC minimization and infection risk reduction; (iv) the use of protocol biopsies to guide treatment duration and (v) management of nonimmune CKD risk factors in patients with LN. These questions were formulated to complement, rather than duplicate, existing international guidelines by addressing areas of uncertainty and specific challenges in the Portuguese context.

Literature search and evidence selection

A targeted narrative literature review was conducted between August 1971 and December 2025 using MEDLINE/PubMed and major guideline repositories. Search terms included combinations of “lupus nephritis”, “systemic lupus erythematosus”, “KDIGO 2024”, “ACR 2024”, “EULAR 2025”, “mycophenolate”, “cyclophosphamide”, “cyclosporin”, “voclosporin”, “tacrolimus”, “calcineurin inhibitor”, “belimumab”, “obinutuzumab”, “rituximab”, “anifrolumab”, “protocol biopsy”, “therapeutic adherence“, “physical activity and exercise” “Vaccination and prophylaxis“ or “cardiovascular risk” in LN.

Priority was given to: (i) international guidelines (KDIGO 2024, ACR 2024, EULAR 2025); (ii) randomized controlled trials and their longterm extensions; (iii) highquality observational cohorts; and (iv) consensus documents from other national or regional societies where relevant. Reference lists of key articles and guidelines were manually screened to identify additional pertinent studies. For the purposes of this position statement, we did not perform a formal systematic review or metaanalysis. Instead, evidence was selected pragmatically, with emphasis on studies most likely to influence current practice (pivotal phase II–III trials, large cohorts, or guidelinedefining work). When multiple sources addressed the same question, higherlevel evidence (randomized trials or guideline summaries) was prioritized over smaller or less rigorous studies.

Classification of statements

To enhance transparency, statements in this document were conceptually grouped into three categories:

1. Guidelinebased statements: recommendations that are directly aligned with KDIGO 2024, ACR 2024, or EULAR 2025 and explicitly reference these documents.
2. Trialinformed statements: suggestions primarily supported by phase II–III clinical trials or robust observational data (e.g., BLISSLN, AURORA, NOBILITY, REGENCY), particularly regarding combination regimens and newer agents.
3. Consensusbased expert opinion: proposals reflecting the collective judgement of the INWG, especially where guidelines diverge, evidence is limited, or national issues such as drug access and reimbursement are central.

For clarity and readability, these categories were not formally graded or labelled at every sentence in the main text; However, we indicate in the narrative when

a recommendation is mainly guidelinedriven or largely based on expert consensus, and we explicitly acknowledge areas where evidence remains limited.

Consensus development process

The consensus process involved all members of the INWG. An initial draft summarizing the evidence and international guidelines was prepared by a core writing subgroup and circulated electronically to all members for comments and proposed statements. Two inperson meetings and several virtual meetings were then held to discuss contentious areas, refine the scope of recommendations, and adapt them to the Portuguese setting, including regulatory and access considerations.

Draft recommendations were discussed item by item. When substantial disagreement arose, revised wording was proposed and members were asked to indicate agreement or disagreement. Consensus was defined a priori as at least 80% agreement among voting members. Statements that did not reach this threshold were further modified and revoted until consensus was achieved or the recommendation was downgraded to a more cautious suggestion. The final version of the manuscript was reviewed and approved by all authors on behalf of the Working Group.

Limitations

This document is intended as a consensus position statement rather than a formal clinical practice guideline. It is based on a targeted, but not fully systematic, review of the literature and does not use a formal grading system such as GRADE. As such, recommendations should be interpreted as expert guidance to support, but not replace, individualized clinical judgement and shared decisionmaking.

MANAGEMENT OF PROLIFERATIVE LUPUS NEPHRITIS

1. Drugs and strategies that minimize LN activity and prevent relapse

The pathophysiology of LN and SLE is complex and heterogeneous, reflecting the involvement of multiple pathological pathways that differ in contribution and severity between patients and evolve throughout an individual's lifetime. Consequently, it remains challenging to determine which therapeutic regimen is best suited for a specific patient at a given time. Precision medicine will progressively evolve towards defining clusters of patients according to the disease-specific pathophysiologic pathways involved, individual genetics and immunological response to drugs. This approach will ultimately allow clinicians to optimize combination treatments, enhancing efficacy while minimizing toxicity.

The previous concept of ''induction'' and ''maintenance'' therapy has been replaced over the last years with a perspective of ''initial'' and ''subsequent'' treatment, where a combination of immunosuppressive agents are used in different regimens to suppress autoimmunity (thus reducing inflammation and preventing relapse) in a continuum, while other measures are taken to control CKD as we will discuss in this paper.[6-9] Besides new therapies that were included in the armamentarium of LN recently (namely belimumab, voclosporin and obinutuzumab), another important aspect of LN management is also changing, which is the possibility to tailor immunosuppression according to histological activity instead of 'clinical activity' as the authors will refer below.[6-10]

I.I. Therapeutic Adherence

Therapeutic adherence is a cornerstone of SLE and LN management, although its importance often remains underrecognized. Studies have reported that low adherence may affect 40%–75% of patients, depending on its definition, and is associated with worse clinical outcomes. The reasons for non-adherence are multidimensional and complex.[11,13] Consequently, different strategies are required to support patients in improving adherence, namely:

- Patient education: providing information regarding the SLE and organ involvement, usual symptoms and how the medication will help reduce them; clarifying indications for all medication (benefits and side effects expected);
- Information flyers covering disease and medication details, as well as patients associations contacts, will help patients to better process information and manage the disease;
- Prolonged visits and interactive encounters with the treating physicians, inviting the patient to ask questions and feel involved in its disease treatment;
- Continuous care by the same physician;
- Medication mobile application to help remind patients to take their medication;
- Prescription interval: adjusted to patient preference and lifestyle;
- Drug levels: can help in starting a meaningful conversation about how to improve adherence;
- Shared decision making: is essential to involve the patient in the disease management, understand its preferences and adjust the treatment accordingly; explaining the rationale for each drug to allow patient empowerment;
- Psychosocial Support and engagement of family members.

I.II. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial drug with immunomodulatory properties. HCQ is recommended

for all lupus patients, as multiple studies have consistently shown its benefits, including lower rates of disease flare and reduction of accrual damage, better control of cutaneous and articular manifestations, reduction of GC dose, advantageous pregnancy profile (with lower risk of relapses, preeclampsia, fetal growth restriction and prematurity), beneficial lipid profile, lower risk of thrombosis, atherosclerosis, and improvement of bone health.[14,15]

Dose should be limited to 5 mg/kg/day (maximum 400 mg) to reduce the risk of ophthalmological toxicity. Smoking should be avoided, as it may reduce the therapeutic efficacy of HCQ.[15]

Patients with estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 should have a 50% dose adjustment. Routine ophthalmologic screening for HCQ retinopathy should be carried out yearly following 5 years of therapy (after 1 year in the presence of a known risk factor, namely eGFR<60 mL/min/1.73 m^2 and doses >5 mg/kg/day).[7-9,14]

I.II.a Position of the INWG on the use of HCQ in treatment of LN

As recommended in LN guidelines, the INWG considers that HCQ shoud be prescribed to all patients with LN that do not have contraindications to its use.[7-9]

I.III. Initial treatment with dual immunosuppression
i.III.a. Cyclophosphamide – National Health Institute or Euro-Lupus nephritis regimens plus Glucocorticoids

Cyclophosphamide (CYC) is an alkylating agent that induces DNA damage, especially in rapidly dividing cells. It has a strong immunosuppressive effect and is used in many immune-mediated diseases. However, significant adverse effects limit its use, particularly severe bone marrow suppression, which is associated with an increased risk of infection and a potential long-term risk of malignancy (especially with cumulative doses > 36 g).[16] Another concern is gonadal toxicity that correlates with CYC cumulative dose and patient's age. Euro-Lupus regimen dose of 3 g is generally safe, but the risk of premature ovarian insufficiency can rise to 50% with cumulative CYC doses of approximately 20 g for females in their twenties, 10 g in their thirties, and 5 g in their forties.[17-21]

The evidence that supports the use of CYC in LN is based on landmark National Institute of Health (NIH) trials during the 1970-1990s, in which the addition of CYC to GC was shown to be superior compared with GC alone or azathioprine (AZA) and GC, in preserving long-term kidney survival in active LN.[22-28] In order to reduce secondary effects of CYC, the Euro-Lupus nephritis (ELN) trial demonstrated that a reduced-dose CYC regimen (3 g) achieved clinical results comparable to those reached with a high dose of CYC, with an improved side-effect profile.[29,30] Although CYC was evaluated mainly in an European cohort in the ELN trial, its efficacy was also confirmed in patients with Asian, African and Hispanic descent, in other studies.[31,32]

The recommended cyclophosphamide-based regimens are outlined below:

- Low-dose CYC (ELN)- pulses of IV CYC, 500 mg every two weeks for a total of six doses (3 g)[29,30];
- High-dose CYC (NIH)- pulse IV CYC (500-1000 mg/m^2 body surface area - BSA) administered monthly for six months. Subsequent dosing should be guided by the leukocyte nadir (10 to 14 days post infusion). If <3500 cells/µL and/or the absolute neutrophil count (ANC) <1500 cells/µL, the dose of the infusion should be reduced by 0.25 g/m^2 BSA or transiently withheld if the counts are very low. On the other hand, if the total white blood cell nadir is ≥3500 cells/µL, the ANC is ≥1500 cells/µL, and the patient has not improved, the dose may be increased by 0.25 g/m^2 BSA. The maximum dose is 1 g/m^2 BSA, although some authors would not exceed 1g per dose.[22-28] CYC dose should be reduced between 20 and 25% of the standard dose if eGFR <60 mL/min/1.73 m^2.

I.III.a.1. Position of the INWG on the use of CYC in the initial treatment of LN

Similarly to KDIGO 2024, ACR 2024 and EULAR 2025 LN guidelines, the IWG considers that a CYC regimen, preferably the low-dose ELN regimen, should currently be reserved for patients with intolerance and non-response to MMF, more aggressive cases of LN or in patients with poor compliance to oral therapy.[7-9] A higher dose CYC regimen (NIH), can also be considered in patients with crescentic glomerulonephritis (GN), rapidly progressive renal failure and severe renal inflammation.[7-9] The evidence of MMF efficacy in such severe patients has not been proved and observational studies have revealed that CYC may be superior in preserving long-term renal function, especially in these patients.[33,34]

I.III.b. Mycophenolate mofetil plus Glucocorticoids

Mycophenolate mofetil (MMF) MPA has a potent cytostatic effect on T- and B-lymphocytes.[35]

Its safety profile is significantly better than CYC, as it does not decrease fertility, causes less cytopenia and does not have an oncogenic effect. However, MMF is teratogenic and is contraindicated in pregnancy as well as during breastfeeding.[36] Dose-related bone marrow suppression can occur and should be monitored closely in particular in the first weeks of therapy. Gastrointestinal symptoms are the most commonly observed adverse effects, but usually resolve with time or dose adjustments. In some cases, symptoms only resolve after switching to enteric-coated mycophenolate sodium (EC-MPS).

Trough levels of MPA can be useful to assess therapeutic adherence, however, its weak correlation with the area under the curve makes it an unreliable indicator to individualize therapy.[37]

The need for safer and less toxic immunosuppressive therapy led to the introduction of MMF in LN. The major evidence comes from the Aspreva Lupus Management Study (ALMS) which compared the NIH CYC regimen dose with MMF (target dose 3 g/day) in patients with LN class III to V. Efficacy and safety profile did not differ in both groups which allowed MMF to be included in the armamentarium of LN. Currently guidelines favour MMF to treat proliferative LN, except in patients with intolerance, poor therapeutic adhesion or more aggressive disease, as specified above.[7-9]

The recommended mycophenolate-based regimens are outlined below:

- MMF (pills 250 and 500 mg) - target dose of 2-3 g/day, divided in 2 to 3 doses, depending on tolerance, adverse effect and severity of LN. In patients with eGFR<25 mL/min/1.73 m2, avoid doses above 2 g/day;
- EC-MPS (pills of 180 and 360 mg) - target dose of 1440-2160mg/day divided in 2 doses.

I.III.b.1. Position of the INWG on the use of MMF in the initial treatment of LN

Similarly to KDIGO 2024, ACR 2024 and EULAR 2025 LN guidelines, the INWG considers that MMF/EC-MPS should be the first line option for the initial treatment of proliferative LN for most patients. Exceptions to this general rule are patients with intolerance, poor therapeutic adherence or more aggressive disease, in which other options, namely with CYC as already discussed, and should be considered.[7-9]

I.IV. Initial treatment with triple immunosuppression

the emergence of new drugs with proven efficacy in the treatment of LN led to an update of the main international guidelines, namely the KDIGO 2024, ACR 2024 and EULAR 2025. Despite differing in the use of first-line triple immunosuppression for all or selected patients, all guidelines recommend the addition of belimumab or voclosporin to standard of care (SoC) as possible options for the initial treatment of proliferative LN.[7-9] Considering the important results from the NOBILITY and REGENCY trials, the INWG feels that obinutuzumab (OBZ) should already be considered as a possible option in the treatment of LN, as incorporated in the EULAR 2025.[8] Although long-term data are needed, OBZ could possibly allow for another important step in GC minimization, and we expectantly wait for the results of the OBILUP study.[38-40]

I.IV.a. Belimumab plus Mycophenolate mofetil or low-dose Cyclophosphamide and glucocorticoids

Belimumab is a fully human IgG1λ monoclonal antibody that binds to the soluble B-cell activating factor (BAFF), inhibiting B-cell survival, differentiation and antibody production. Although generally well tolerated, cases of suicidal ideation have been reported, though not consistently. Therefore, it should be used with caution in patients with depression. The most frequent adverse events reported are bacterial (bronchial and urinary) and viral infections, diarrhoea, nausea and leukopenia.[41-43]

Based on the BLISS 52 and BLISS 76 randomized controlled trials (RCT), belimumab became the first biological agent approved to treat patients with SLE in 2011.[43,44] Besides these RCT, real-world data has shown that belimumab is effective in reducing SLE clinical and serological activity (particularly musculoskeletal and mucocutaneous involvement), the incidence of flares (severe and non-severe), *de novo* LN and long-term accrual damage, while allowing GC sparing.[45-46]

Regarding LN, the evidence of its effectiveness in renal disease comes from the phase III Belimumab International Study in LN trial (BLISS LN). It evaluated the efficacy of belimumab as an add-on to SoC (MMF or CYC–followed by AZA) in patients with LN classes III to V, with proteinuria >1g/day. In this study, the primary (primary efficacy renal response - PERR) and major secondary endpoints (CRR) were achieved significantly more in the belimumab group (43% *vs* 32% odds ratio 1,6; *p*=0.03; 30% *vs* 20%; odds ratio 1,7; *p*=0.02) at week 104. The risk of a renal-related event or death was also lower among patients taking belimumab (HR 0.51; *p*=0.001) and benefits persisted during the open label extension of 28 weeks of BLISS LN. Subgroup and post-hoc analyses revealed that benefits of belimumab in kidney outcomes (PERR and CRR) were consistent in newly diagnosed and relapsed patients, with or without GC pulses at induction and improved histological remission. However, response was mostly driven by the MMF subgroup and proliferative LN classes (not pure class V), especially in patients with urine protein/creatinine ratio under 3 g/g. Nevertheless, the risk of kidney-related events or death, LN flares or sustained 30% or 40% decline in eGFR were reduced in the overall population, independently of LN class or degree of proteinuria.[47-51]

Considering these results, EULAR 2025, KDIGO and ACR 2024 LN guidelines all recommend (with different strength) the triple immunosuppression regimen with belimumab added to low-dose CYC or MMF and GC as a possible option to treat proliferative LN, especially in patients with non-nephrotic proteinuria, repeated kidney flares, extra-renal manifestations or at high-risk for progression to kidney failure due to severe chronic disease.[7-9] Risk of overtreating patients and costs associated are the main limitations to consider this triple therapy in all proliferative LN patients. One can also argue that reducing the risk of relapse will decrease immunosuppression burden in the disease course and subsequently overall cost. In this regard, the ACR 2024 guidelines already contemplate this option upfront.

However, we must emphasise that, currently, in Portugal, belimumab may be prescribed only for SLE patients with

active disease *(SELENA-SLEDAI>10)* despite optimized SoC therapy, active immunological activity (dsDNA titres>30 IU/mL and low complement), and without renal or central nervous system involvement. The co-payment for LN indication was not approved by Portuguese regulatory authorities (INFARMED), despite being endorsed by all major international guidelines. The INWG believes that this position should be reassessed by INFARMED, to ensure that Portuguese patients have the same opportunities as other European patients. Meanwhile, the exclusion of ''renal involvement'' in the indication of belimumab will probably receive a positive review by INFARMED and will be removed in the near future.

The recommended belimumab-based regimens are outlined below:

- Intravenous belimumab – 10 mg/kg q2weeks x3 doses, then 10 mg/kg q4 weeks; 1-hour infusion
- Subcutaneous belimumab – 400 mg weekly x 4 doses, then 200 mg weekly

Dose adjustment is not required in patients with renal impairment. Hypersensitivity reactions may occur; therefore, an antihistamine (with or without analgesic) can be given in the first two administrations, which should take place under clinical supervision for several hours. Belimumab is not approved for pregnant or lactating patients, although its use has been increasingly reported and could be considered in selected cases. No prophylaxis is recommended.

I.IV.a.1. Position of the INWG on the use of belimumab in the initial treatment of LN

The INWG considers that belimumab is an important addition to the therapeutic armamentarium of LN classes III/IV (with or without associated class V) and should particularly be considered in patients with high scores of histological LN activity *(not crescentic GN),* non-nephrotic proteinuria, repeated kidney flares, high-risk for progression to kidney failure, extra-renal manifestations with increased risk of GC-related adverse events and in patients with sub-optimal renal response at 3 to 6 months (namely accompanied by immunological activity and extra-renal manifestations that may respond to belimumab). Although its use upfront can be argued in all patients, the positioning of the INWG is to preferably consider this option in patients with frequent SLE relapses, extra-renal manifestations and in which GC minimization is a priority (due to previous steroid-related events or comorbidities aggravated by GC).

I.IV.b MMF Plus Calcineurin Inhibitor and glucocorticoids

Calcineurin inhibitors (CNIs) such as cyclosporine A (CsA), tacrolimus (TAC) and voclosporin (VCS) are immunosuppressive agents that are used to treat SLE and LN. They act by inhibiting calcineurin phosphatase activity and suppressing NFAT-mediated transcription of cytokine genes, which are critical for T-cell activation, proliferation and differentiation. Additionally, CNIs stabilize the podocyte actin cytoskeleton and cause afferent arteriole vasoconstriction, thereby reducing proteinuria by non-immune mechanisms.[7-8,52-53] Comparing the three CNI, TAC is more potent than CsA, with more reliable trough levels and seems to also inhibit B-cell activation, antibody production and possibly reduce the generation of T follicular helper cells.[53] VCS is also up to 4-fold more potent than CsA and has a favourable metabolic, pharmacodynamic and safety profile, reducing the risk of diabetes, dyslipidaemia and nephrotoxicity, eliminating the need of blood level monitoring.[54,55] Overall, CNIs adverse events can be significant, namely hypertension, dyslipidaemia, diabetes (especially with TAC), gum hyperplasia, nephrotoxicity and neurotoxicity (more frequent with TAC), with VCS having the safest profile. Careful blood level monitoring (of CsA and TAC) should occur in patients treated with drugs affecting CYP3A4/5 metabolism or P-gp transport. In patients taking VCS, those drugs should be avoided.[54,55]

Regarding the use of CNIs in LN, most evidence comes from Asian RCT and is predominantly with TAC. Two meta-analyses of Asian RCTs comparing multitarget therapy (TAC + MMF + GC) versus iv CYC for induction therapy in LN patients found that multitarget therapy was superior in achieving CRR or partial remission (PR) (RR: 2.29; 95% CI: 1.45–3.62; $p = 0.0004$).[56,57] In a retrospective cohort study, Yap *et al* found that the addition of TAC (target plasma levels of 4–6 mg/L) in patients with class III/IV/V LN with persistent proteinuria despite MMF+GC could increase the possibility of CRR and PR.[58]

Regarding VCS, the evidence that supports its use in LN emerged from two clinical trials that compared the efficacy and safety of VCS as add-on to SoC with MMF(2g) and a very short GC regimen, in patients with class III-IV (+V or V alone), urine protein-creatinine ratio UPCR ≥1.5 g/g (or ≥2 g/g if pure class V), and eGFR >45 mL/min/1.73 m^2 at screening - AURA-LV (phase II) and AURORA 1 (phase III) plus its 2-year extension trial (AURORA 2).[59-62] The AURA-LV defined the recommended dose of VCS (the low-dose of 23,57mg BID) in the phase III trials, in which almost 20% more patients in the VCS group achieved CRR at 52 weeks (41% *vs* 23%; OR=2.65). These effects persisted in the 24-months extension of the AURORA 1 trial (AURORA 2 - CRR 50.9% in the VCS *vs* 39.0% in the placebo; OR 1.74; 95% CI 1.00–3.03). Renal function was more stable in the VCS group (eGFR slope of −0.2 mL/min/1.73 m^2 in the VCS group *vs* −5.4 mL/min/1.73 m^2 in the control group), although the dose of VCS for a proportion of the patients was reduced over time, which may have influenced eGFR.[61,62] Although the primary outcome was reached in the overall population, it is important to note that statistical significance was not achieved in some subgroups, namely in patients from Europe, South Africa

or North America, white patients, pure class V LN and when MMF was not being used at screening or when its maximum dose was below 2 g/day during the study. Additionally, there was no statistical difference between the VCS and the placebo groups with regard to immunology parameters serum complement and ds-DNA antibodies, casting doubts about whether the effectiveness of VCS is related to its immune effects.[59-62]

The lack of strong evidence for multitarget therapy with CsA or TAC in non-Asian LN patients led guidelines to consider these CNIs as second line options in triple immunosuppressive regimens.[7-9] Considering TAC has more reliable blood monitoring and stronger evidence than CsA, this CNI should be preferred if VCS is not available. As referred previously, VCS is the only CNI with significant evidence in LN derived from phase III RCTs and, possibly, should be the recommended CNI to treat proliferative LN. Considering its rapid effect on proteinuria reduction even in severe proteinuria (related to more prominent podocytopathic injury), guidelines favour the addition of VCS to MMF regimen in patients with eGFR > 45 mL/min/1.73 m^2 and nephrotic-range proteinuria or for those with low tolerance to high dose of MMF and who want to avoid CYC.[7-9]

The recommended CNI-based regimens are outlined below:

- TAC: start TAC 0.05 to 0.1 mg/kg/day or 2-4 mg/day in 2 divided doses, titrated to a target blood concentration of 4-6 ng/mL;
- CsA 1-3 mg/kg/day or up to 400 mg/day in 2 doses.[63]
- VCS 23.7 mg (3 capsules of 7.9 mg) twice a day (BID).

Dosage should be stopped or reduced if serum creatinine increases by more than 30%.

There is no consensus on the target blood levels for TAC or CsA.

I.IV.b.1. Position of the INWG on the use of CNI in the initial treatment of LN

As EULAR 2025, KDIGO and ACR 2024 LN guidelines, INWG considers that this therapeutic regimen could be considered in patients with eGFR > 45 mL/min/1.73 m^2 and nephrotic-range proteinuria or for those with low tolerance to high dose of MMF and who want to avoid CYC.

I.IV.c. Mycophenolate mofetil and obinutuzumab plus glucocorticoids

Obinutuzumab (OBZ) is a recombinant, humanized type II anti-CD20 IgG1 monoclonal antibody, glycoengineered to enhance antibody-dependent cell-mediated cytotoxicity and phagocytosis inducing a more prolonged and efficacious depletion of CD20 B cells at blood and tissue level than RTX.[64,65]

The most frequent adverse effects are infusion related reactions. Reactivation of hepatitis B virus can occur, as such, all patients should be screened and start antiviral therapy if previous infection is diagnosed. JC virus infections that can lead to progressive multifocal leukoencephalopathy have been reported, as well as an increased prevalence of low IgM, but not low IgG, compared with baseline.[64-66]

Evidence of OBZ efficacy in the treatment of LN comes from 2 trials, the phase II NOBILITY trial (with its extension of 2 years) and the phase III REGENCY trial.[38,39] Both trials evaluated patients with active proliferative LN (class V) receiving OBZ as add-on to SoC with a reduced dose GC regimen. The NOBILITY trial achieved its primary endpoint at 52 weeks (CRR 35% in the OBZ group *vs* 23% in the placebo group) and overall renal responses persisted at 104 weeks, even in patients with nephrotic range proteinuria and particularly in patients with class IV LN. Post-hoc analysis revealed that the OBZ group had favourable kidney outcomes at 104 weeks, with a decreased incidence of LN flares or loss of 30%-40% eGFR and the attenuation of eGFR slope (difference: 4.1 mL/min/1.73 m^2/year; p=0.043). Additionally, those outcomes were observed along with GC sparing.[38, 39, 69]

The REGENCY phase III trial also achieved its primary endpoint (CRR at 76 weeks: 46.4% in the OBZ group *vs* 33.1% p=0.02) and secondary outcomes (CRR at 76 weeks with GC<7.5 mg/day 42.7% in the OBZ group *vs* 30.9% p=0.04; UPCR <0.8 in 55.5% patients OBZ group *vs* 41.9% p=0.02). There was a general trend to a favourable renal response in all subgroup analysis, however only reaching statistical significance in patients with higher proteinuria (>3 g/24h), higher immunological activity (higher dsDNA titer and lower complement levels), classes IV and V LN and newly diagnosed patients. The OBZ group had a greater reduction of C3, C4 and dsDNA antibodies, and more patients had complete CD19-positive B-cell depletion, compared to placebo. No unexpected safety signals were identified. More serious adverse events, mainly infections and events related to coronavirus disease 2019, occurred with OBZ than with placebo.[38, 68]

To explore the ability of OBZ to substitute GC, the ongoing OBILUP trial, will evaluate the non-inferiority of OBZ and MMF regimen compared to SoC (MMF+GC).[69]

The results of the REGENCY trial were recently published and the 2025 EULAR recommendations for the management of SLE with renal involvement already recognize the combination of OBZ plus MMF as an additional therapeutic option. The strong evidence presented by these trials supports its use in the treatment of proliferative LN, especially refractory LN.[8,9,70,71]

It was approved in October 2025 by FDA for the treatment of adult patients with active LN who are receiving standard therapy and by the European Medicines Agency (EMA) for the treatment of adult patients with active Class III or IV, with or without concomitant Class V LN in combination with MMF. Additionally, EULAR 2025 guidelines also recommend its use especially in patients with poor prognostic factors.[9,72,73]

The recommended OBZ-based regimen is outlined below:

- OBZ: iv infusion of 1000 mg on day 1 and weeks 2, 24, 26, and 52, with or without a dose at week 50. Patients should receive prophylactic treatment with paracetamol, an anti-histaminic and low-dose methylprednisolone (80 mg) or hydrocortisone (100 mg) 30–60 minutes prior to the drug, to reduce the risk of infusion-related reactions.

I.IV.c.1 Position of the INWG on the use of OBZ in the initial treatment of LN

In Portugal, OBZ is only approved for haematological neoplasms. Subsequently its prescription can only occur under exceptional access mechanisms *or "off label"* in selected patients. It is important to note that long-term data regarding OBZ effectiveness and safety are lacking. However, considering recent RCT and updated EULAR 2025 guidelines, the INWG considers that OBZ can be a valuable option in patients with proliferative LN. As such, we defend that OBZ could be considered in selected patients with therapy adhesion issues, severe LN with nephrotic proteinuria, refractory LN, and those with GC complications, extra-renal manifestation and significant immunological activity.

I.V. Glucocorticoids regimens

GC have always been part of LN treatment, but during the last decades, efforts have been made to reduce their cumulative dose to decrease toxicity. Consequently, successive trials have adopted varying GC regimens, and the introduction of triple immunosuppressive strategies (namely in the VCS and OBZ trials) has allowed for marked reductions in GC exposure.[74] In this context, the KDIGO guidelines outline three GC schemes, which can be tailored based on SLE/LN disease severity and the selected immunosuppressive approach (dual versus triple therapy) (Table 1).

Traditionally, methylprednisolone (MP) iv pulse therapy has been used to achieve non-genomic GC effects (besides genomic GC effect) and allow rapid control of SLE disease activity. However, and considering this activation starts at prednisone equivalent dosages of 100 mg, and reaches its maximum around 250 to 500 mg, KDIGO 2024 guidelines now recommend using lower doses of MP (250-500 mg for 1-3 days) and then proceed using a regimen of prednisolone 0.5 (preferably) to 1 mg/kg/day according to disease severity. The use of MP pulse less than 1.5 g in total has been associated with lower risk of infection.[75,76] Furthermore, genomic effects are activated with low-dose GC (7.5 mg prednisone equivalent per day) and cytoplasmic GC receptors become progressively saturated with daily doses above 30 to 50 mg, which imply probably low benefit from doses above 60 mg/day.[77]

I.V.a. Position of the INWG on the use of GC in the initial treatment of LN

The INWG considers that minimization of GC exposure is a key aspect SLE management (see discussion chapter III).

In line with the 2024 KDIGO guidelines, the INWG similarly recommends a GC regimen based on low-dose iv MP pulses (250-500 mg/day up to three days) followed by a reduced dose scheme.[7-9]

However, it must be emphasized that many factors should be taken into account, namely patient's preference, use of dual or triple immunosuppressive regimen, SLE and LN severity, GC-related complications and underlying diseases that strengthen the need of GC sparing.

I.VI. Subsequent treatment with dual and triple immunosuppression

Regarding subsequent treatment of proliferative LN, the INWG follows the international guidelines recommendations.[7-9]

Following completion of initial therapy, patients should maintain MMF or start MMF if CYC was administered, for a total duration of treatment of at least 3 years. In patients treated with triple immunosuppressive therapy, belimumab and CNI should be maintained for 2.5-3 years.[7-9]

The optimal duration of total immunosuppression is not known and should be individualized to minimize the risk of long-term complications while maintaining adequate disease control and reduced risk of flares.

The KDIGO guidelines suggest tapering GC to the minimum possible dose, ideally with complete discontinuation if CRR is achieved and sustained for at least 12 months.

In patients considering pregnancy, MMF can be switched to AZA.

I.VI.a. Role of Protocol Biopsies to safely reduce immunosuppression in selected patients

Several studies from Ana Malvar group have long revealed that markers of LN (e.g., proteinuria <500 mg/day) do not reliably correlate with histological findings. A study where biopsies were performed at diagnosis and at 6 months, showed that one third of patients with proteinuria <500 mg/day still had high histological activity, while on the contrary 62% of patients with proteinuria >500 mg/day had no sign of histological activity.[10] These important findings prompted another study by the same group, which evaluated the role of protocol biopsies performed at 4 years of treatment and every 2 years thereafter, with the aim of reducing or discontinuing therapy only in patients without histological activity. The cohort included 76 Hispanic patients, among whom the incidence of LN flare was reduced to 9.2% after approximately 8 years of follow-up — a significantly lower relapse rate than typically reported, particularly in Hispanic populations (≈30%–50%).[78]

Another opinion article, developed by experts from Europe and Americas, proposed an algorithm for immunosuppressive therapy withdrawal in patients with LN. It included a biopsy at one-year in patients with PR to define which individuals should either intensify or continue tapering therapy, followed by a biopsy at 36–42 months

to select those who could be considered for treatment discontinuation.[79]

A "liquid biopsy" with non-invasive biomarkers would be ideal to guide safe immunosuppression tapering, however, it is not yet available. As such, conventional biopsy remains valuable for individualizing management at one year in patients who have not achieved CRR, and for safely considering therapy withdrawal after four years of total LN treatment, thereby reducing the risk of LN flares (particularly in relapsing patients).

I.VI.a.1. Position of the INWG on the role of Protocol Biopsies in the management of LN patients

The INWG considers that in experienced Nephrology Units, with low procedure-related complication rates, a renal biopsy at one year in patient with PR or at three to four years of treatment could be a valuable approach to individualize therapy withdrawal and reduce the incidence of LN flares and CKD in the long-term.

II. Therapies Targeting Non-Immune Factors of CKD in LN

While immune-mediated mechanisms remain central to the pathogenesis of LN, non-immune factors, such as hypertension, dyslipidaemia, hemodynamic stress, and cardiovascular comorbidities, play a significant role in the progression of CKD and contribute to cardiovascular (CV) disease, a leading cause of mortality in patients with LN. Addressing these factors is essential to improve survival and preserve kidney function[79,80] (Table 2). The KDIGO 2024 guidelines emphasize the importance of evaluating and managing these factors, which contribute to renal damage irrespective of immune activity.[7] Strategies such as optimizing blood pressure control, minimizing albuminuria, and addressing metabolic syndrome are foundational in slowing CKD progression.[82]

II.I. Physical activity and exercise

Non-pharmacological interventions can have a significant impact in improving the overall health in patients with SLE, namely physical activity (PA - any bodily movement produced by skeletal muscles that results in energy expenditure) and exercise (PE - subset of physical activity purposeful, planned and repetitive with the goal of maintaining or improving physical fitness). Studies have shown that aerobic and resistance exercise programs can improve aerobic capacity, reduce cardiovascular risk, and enhance strength and physical function in patients with SLE, while also decreasing fatigue and depression, and providing significant health-related quality of life (QoL) benefits.[100,101]

In CKD patients, PA and PE can also reduce CV risk, improve markers of physical function, QoL and even delay CKD progression.[102,103]

These results led to the development of the Recommendations for PA and PE in persons living with SLE: consensus by an international task force.[101] Ideally an individualized assessment (namely CV, rheumatological/orthopaedical) for personalized PA/PE program should be done in all SLE patients. Both aerobic and resistance training programmes are recommended, with a gradual increase in frequency and intensity. Considering the importance and potential benefits of PA/PE in patients with SLE and LN/CKD, the INWG lists the 15 recommendations provided by the international task force (Table 3).[101]

III. Measures that reduce the risk of infection

Despite the overall improvement of care and prognosis, infection remains a significant cause of morbidity and mortality in SLE patients, particularly in patients with LN, with strong connection to disease activity and immunosuppressive drugs exposure.[104-106]

A meta-analysis reviewing a total of 469 570 patients with SLE and 6 528 441 non-SLE/general population/healthy controls, found a 2 to 6-fold increase in the relative risk of infectious events in adult patients with SLE compared with the general population or healthy controls. The pooled risk in SLE patients for overall severe infections was 3.0-fold; 6.1-fold for tuberculosis, 2.6-fold for pneumonia and 2.5-fold for herpes zoster.[106]

This epidemiological data mandates that measures to reduce the infectious risk in this population should be strongly considered, with particular emphasis on rational use of immunosuppression and GC, vaccination and prompt identification and treatment of infection.

III.I. Lowering GC dose

There is a dose-response relationship between the GC dose and the frequency of infections, with higher GC doses being associated with an increased risk of serious infections. However, a clear relationship also exists between GC dose and renal response, and it is the clinician's challenge to find, for each individual patient, the adequate balance, to maximize effectiveness while minimizing side effects.

In a recent systematic review and meta-analysis of the control arms of RCTs with LN patients, starting with a prednisone-equivalent dose of 0.4-0.7 mg/kg/day resulted in a CRR rate of 18%-25% at 6 months, with minimal increases in the risk of infections or death; in contrast, higher starting doses >0.7 mg/kg/day of prednisone-equivalent, yielded higher CRR responses (up to 35% at 1.0 mg/kg/day), but with a disproportionately higher increase in the risks of death and serious infections.[108] This meta-analysis suggests, however, that rapid tapering (to ≤7.5 mg/day by week 16) in patients receiving MMF or CYC, although reducing the risk of serious infections, may reduce renal response at 6–12 months.

Another pooled analysis of the controlled arm of similar high-quality RCTs with LN patients revealed no significant differences in the 12-month renal responses in patients receiving initial low-dose (0.5 mg/kg/day) oral GC after intravenous MP pulses compared with those receiving

higher doses (1.0 mg/kg/day), with lower adverse event rates in those receiving low-dose.[109]

Although each patient's specific clinical condition must always be taken into account, the presented data seems to convey as a general rule, that a low-dose GC regimen should be preferred: IV MP pulses (250-500 mg) followed by oral prednisolone/prednisone (0.35-0.5 mg/kg/day).

III.II. Screening for latent infections, Vaccination and Prophylaxis

The 2021 KDIGO recommendations evaluating the risks of infections, vaccinations and prophylaxis and the EULAR 2022 recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases are generally followed in the Portuguese clinical setting and therefore supported by the INWG.[110,111]

Before initiating immunosuppression, the INWG strongly recommends protocol screening for latent infectious diseases and, when appropriate, referral to specific consultations.

Patients should be screened for syphilis, HIV, hepatitis B and C, latent tuberculosis, and parasitological stool screening when there is a history of residency or travelling to a tropical country (infection with *Strongyloides stercoralis* should be specifically ruled out in high-risk patients). Serologies for Varicella Zoster virus (VZV) should also be performed, and non-immune patients should be informed about post-exposure prophylaxis following contact with VZV.

Vaccination is a key strategy to reduce infections in SLE patients.

Recommended vaccines include pneumococcal, recombinant VZV, seasonal influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis A and B, and human papillomavirus vaccines. It is crucial to avoid live virus vaccines (measles, mumps, varicella, rotavirus, yellow-fever), as they are contraindicated in patients undergoing immunosuppressive agents; if necessary, their administration should be deferred until the prednisone dose is <20 mg/day and the immunosuppressive agents are stopped for at least 1-3 months and performed under expert supervision.

For patients that will presumably be treated with anti-CD20 therapies, inactivated vaccines should ideally be completed at least 2 weeks prior, and any live-attenuated vaccines completed a minimum of 4 weeks before commencing treatment.[111,112] After treatment initiation, further vaccination should be delayed for at least 6 months. In patients receiving maintenance RTX (e.g., every 6 months), vaccination should be administered as close as possible to the end of a RTX cycle, and the subsequent RTX dose delayed for at least 2 weeks, if clinically possible.[111,112] The exception to these general rules, because of its seasonal nature, is the influenza immunization that is recommended to be given on schedule to patients receiving RTX or any other type of immunosuppression.[111,112]

Based on the 2021 KDIGO guidelines, we suggest that treatment with trimethoprim-sulfamethoxazole (or alternative if intolerant) should be considered in patients receiving high-dose prednisone (>20 mg/day) or other immunosuppressive agents such as RTX or CYC.

IV. Old and New Drugs in the treatment of LN

IV.I. Rituximab

RTX is an IgG1 monoclonal antibody (mAb) that targets CD20 antigen. It induces B cell depletion, except for stem cells and early B-cell precursors in the bone marrow or mature plasma cells, as these cells do not express CD20.[113]

The most frequent adverse events are similar to OBZ (section I.IV.c.) and these patients should follow strategies to minimize infectious risk as described in section III.II. Repeated courses of RTX may be associated with hypogammaglobulinemia, which in turn is linked to an increased risk of infection.[114-123]

Although often used to treat LN worldwide, RTX efficacy in LN has not been supported by RCT, as the multinational Lupus Nephritis Assessment with RTX (LUNAR) study did not demonstrate superiority in CRR when RTX was added to SoC.[114] A possible explanation is the limited efficacy of RTX in achieving complete depletion of peripheral and tissue B cells. A post-hoc analysis of the LUNAR trial found that patients with complete B cell depletion had a higher renal response at 52 and 78 weeks compared with those who did not.[124] This negative result contrasts with encouraging results from other clinical trials that validated a therapeutic role for RTX in selected patients, including refractory or frequently relapsing patients, patients who do not tolerate standard therapy, or when steroid-sparing is attempted.[125-140]

Evidence supporting the use of RTX for refractory LN derives from open-label observational studies and real-world data that have reported response rates of 50%–80% and a meta-analysis of 31 studies with 1112 patients that showed CRR and PR rates of 46% and 32%, respectively, after RTX was added.[125-140] Additionally, a regimen without maintenance GC that used RTX to achieve GC sparing was evaluated in the RITUXILUP study. Patients with active LN were treated with RTX 1 g and MP 500 mg i.v. on days 1 and 15 and were maintained on MMF (maximum dose 1.5 g twice per day) without GC. By 52 weeks, 52% of patients achieved CRR and 34% achieved PR.[125]

Although RTX is not approved by the FDA for the treatment of LN, all guidelines recommend its use to treat refractory LN.

The recommended RTX-based regimens are outlined below:

- RTX: The typical dosage regimen for LN involves 1 g on days 0 and 15, but the regimen 375 mg/m2 once weekly for 4 doses can also be used. Premedication with GC, antihistamines, and acetaminophen is recommended to mitigate infusion reactions.

Serum immunoglobulin levels (IgG, IgM, and IgA) should be obtained at least before each retreatment. If serious infection or repeated infections occur, particularly with low Ig levels, intravenous Ig repletion should be contemplated.

IV.I.a. Position of the INWG on the use of RTX in the treatment of LN

The INWG considers that RTX can be a valuable option in selected patients, including refractory or frequently relapsing LN, patients who do not tolerate standard therapy, or when steroid-sparing is attempted. In cases of rapidly progressive GN or crescentic GN combination therapy with CYC based-regimen could allow CYC sparing if OBZ is unavailable.

IV.II. Anifrolumab

Anifrolumab (ANI) targets the type I interferon (IFN) signalling pathway by specifically blocking the IFNAR1 subunit of type I IFN receptor, which is known to be involved in LN pathogenesis.

ANI most reported adverse effects include viral infections (herpes zoster, influenza), respiratory and urinary tract infections and infusion-related reactions.[140-143]

ANI is indicated for the treatment of patients with moderate to severe SLE receiving standard therapy, based on the results of two phase III RCTs, Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)- 1 and TULIP- 2. In both studies, ANI was associated with improved cutaneous lupus erythematosus disease area and severity index (CLASI) as well as British Isles Lupus Assessment Group-based composite lupus assessment (BICLA) response. Reduction in oral GC dose and flare incidence was also observed.[141-143]

Evidence supporting the use of ANI in LN derives from the phase II ramdomized controlled TULIP LN trial, which evaluated the safety and efficacy of two ANI dosing regimens- an intensified regimen (IR; 900 mg for the first three doses followed by 300 mg every 4 weeks) and a basic regimen (BR)- compared with placebo, all on top of SoC in patients with LN. Although the primary endpoint was not achieved (improvement of proteinuria) at week 52, more patients on the IR attained CRR response at Week 104 compared with those on BR or placebo (27.3% *vs* 18.6% and 17.8%), along with sustained GC tapering and better improvement of eGFR in the ANI groups. Pharmacokinetic data showed that, due to increased drug clearance, a higher ANI dose was required to achieve adequate drug exposure in patients with active LN, compared with patients with non-renal SLE.[144-145]

These results led to the Phase 3 Study of ANI in Adult Patients with Active Proliferative Lupus Nephritis (IRIS) that will further evaluate the role of IR of ANI in proliferative LN.[146]

ANI may be administered using the following dosing regimen:

- ANI: The recommended dose is 300 mg, administered as an iv infusion over a 30-minute period, every 4 weeks. In patients with a history of infusion-related reactions, premedication (e.g., an antihistamine) may be administered before the infusion of anifrolumab.

IV.II.a. Position of the INWG on the use of ANI in the treatment of LN

Although the INWG considers that ANI does not have sufficient evidence to be recommended in LN, the INWG considers that ANI could be an option as a complement to SoC, especially in patients with refractory cutaneous disease and the need of GC sparing, with a possible benefit to treat LN itself.

V. Consensus and practical recommendation

Defining the optimal treatment for LN remains challenging, and to date, tools for a personalized and targeted therapy are still lacking. Consequently, treatment decisions rely primarily on clinical data and patient preferences. It is important to emphasize that nephrologists managing these complex patients should ideally be integrated into multidisciplinary teams, where a global and holistic approach facilitates the selection of the most appropriate treatment regimen.

Following a systematic multiorgan assessment at the moment of the LN flare and a careful review of the patient's history of treatment and response, the INWG lists a series of factors to assess in order to individualize therapy.

Factors to consider in the choice of regimen for LN

- Age, fertility (family planning), cumulative dose of CYC;
- Therapeutic adherence (e.g., iv therapy preferred if history of non-adherence);
- Organ involvement (which organs and specific severity of each organ involvement);
- Nephrotic vs non-nephrotic range proteinuria;
- Immunological activity and its persistence in the disease course;
- Severity of LN (higher NIH activity scores, crescentic or RPGN, nephrotic proteinuria);
- Histological chronicity scores (probability of progression to CKD);
- Previous renal flares or systemic flares (need to control long-term SLE activity);
- Previous response to immunosuppressive agents (complete or partial);
- Patient's preference;
- Infection risk;
- Comorbidities: cardiovascular disease, obesity, diabetes, hypertension;
- Malignancy history;
- Tolerance to GC/ risk of steroid-related toxicity;
- Cost and drug availability.

The decision to choose triple immunosuppressive therapy upfront is debatable as reflected in guidelines: the EULAR 2025 and KDIGO 2024 guidelines support that it could or should be considered according to patients' characteristics or poor prognostic factors (practice points); while the ACR 2024 LN guidelines recommend it should be the first option for all patients. Arguments that favour the upfront use include the need to increase response rate and reduce nephron loss and CKD progression in the long term, which dual therapy regimens have not been able to adequately achieve. Furthermore, triple immunosuppression regimens allow GC sparing, an unmet need that has not been achieved with SoC. Counterarguments include the possibility of overtreating less severe cases that would otherwise respond to SoC, their high cost and the lack of long-term data regarding triple regimens.

As such, the INWG considers that all options could be considered upfront, but individualization is crucial, preferably following a multidisciplinary discussion. It is important to underline that lupus is a multisystemic disease and the considered therapy regimen should be chosen to best fit the treatment of all organs involved while considering the patient-specific treatment-response history and preferences.

The INWG presents practical algorithms for selecting initial and subsequent immunosuppressive therapies and summarizes patient characteristics that may help guide the choice of the most appropriate treatment regimen (Figs. 1 and 2). It should be emphasized that these treatment algorithms, although based on majorminternational guidelines and clinical trial data, reflect the expert consensus of the INWG on the management of proliferative LN.

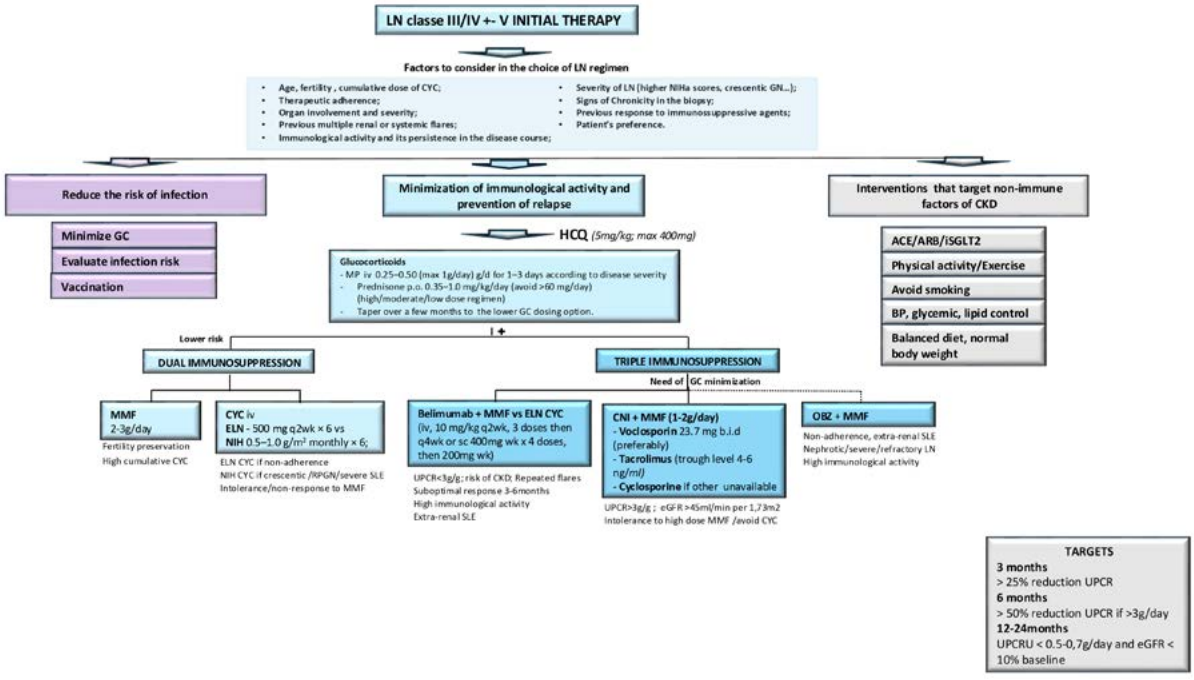

Figure 1. Initial therapy- LN classe III or IV ±V.
Adapted from KDIGO 2024, ACR 2024 and EULAR 2025 guidelines and positioning of the INWG
Angiotensin-converting enzymes inhibitors (ACE); angiotensin II receptor blockers (ARB); blood pressure (BP); calcineurin inhibitor (CNI); chronic kidney disease (CKD); cyclophosphamide (CYC); eurolupus nephritis trial (ELN); glomerulonephritis (GN); glucocorticoids (GC);); inhibitors of sodium-glucose cotransporter 2 (iSGLT2); lupus nephritis (LN); methylprednisolone (MP); mycophenolate mofetil (MMF); National Institute of Health (NIH); obinutuzumab (OBZ); rapidly progressive GN (RPGN) systemic erythematous lupus (SLE); urine protein creatinine ratio (UPCR);

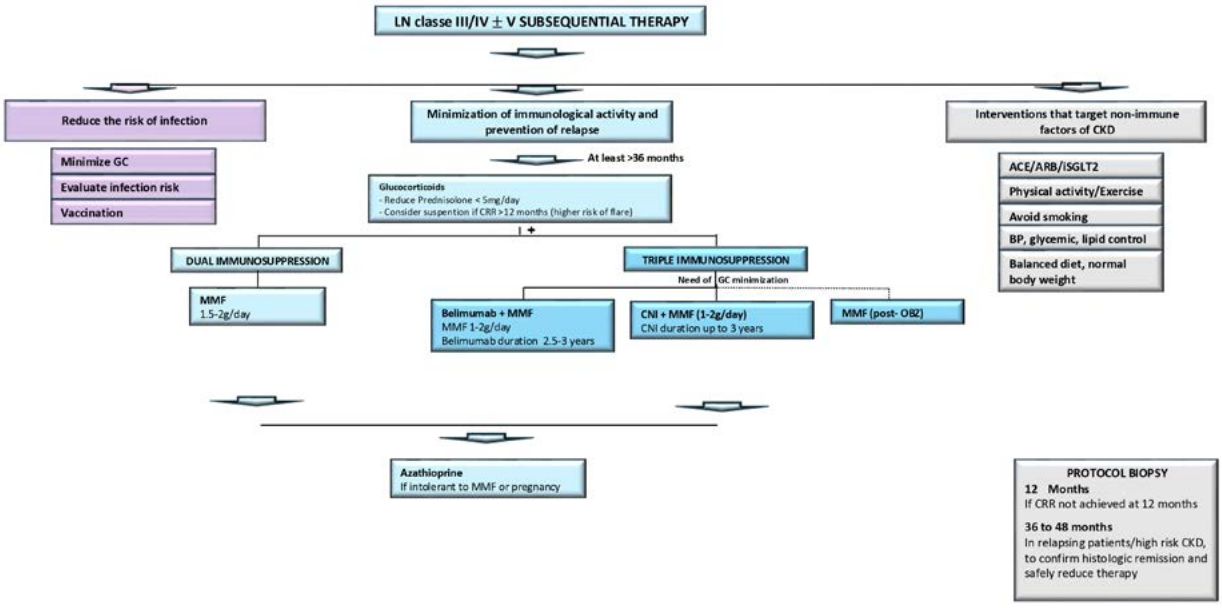

Figure 2. Subsequential therapy- LN classe III or IV ±V.
Adapted from KDIGO 2024, ACR 2024 and EULAR 2025 guidelines and positioning of the INWG
Angiotensin-converting enzymes inhibitors (ACE); angiotensin II receptor blockers (ARB); blood pressure (BP); calcineurin inhibitor (CNI); chronic kidney disease (CKD); complete renal remission (CRR); glucocorticoids (GC); inhibitors of sodium-glucose cotransporter 2 (iSGLT2); lupus nephritis (LN); mycophenolate mofetil (MMF); obinutuzumab (OBZ);

INITIAL TREATMENT

Dual immunosuppression with MMF and GC should be considered, especially in the following patients:

1. Newly diagnosed LN with less clinical and histological severity (Expert consensus)[7-9];
2. Good adherence and need for fertility preservation[7-9];
3. Significant CYC cumulative dose[7-9];

Dual immunosuppression with CYC and GC should be considered, especially in the following patients:

1. Intolerance and non-response to MMF[7-9];
2. Poor compliance with oral therapy[7-9];
3. Higher clinical or histological activity with rapidly progressive GN (consider NIH high dosing protocol) (Expert consensus)[7-9];

Triple immunosuppression that includes belimumab, could be particularly considered in the following patients:

1. LN histological classes III or IV +/- V, with baseline UPCR <3 g/g[7-9];
2. Previous kidney flares[7-9];
3. High scores of histological LN activity (not crescentic GN); *(Expert consensus)*
4. High-risk for medium/long-term progression to kidney failure due to CKD (histological chronicity, persistent proteinuria and persistent immunological activity) (Expert consensus)[7-9];
5. Sub-optimal renal response at 3-6 months, namely accompanied by immunological activity and extra-renal manifestations that may respond to belimumab; *(Expert consensus)*
6. Frequent non-renal relapses; *(Expert consensus)*
7. Extra-renal manifestations (skin, joints, serositis…) with intense or previously persistent serological activity; *(Expert consensus)*
8. Increased risk of GC-related adverse events that imply the need of steroid-sparing strategies (e.g., high previous cumulative dose of steroids or steroid toxicity, diabetes, obesity, osteoporosis, psychiatric disorders…); *(Expert consensus)*

Upfront to be contemplated, especially in patients with criteria 6,7 and 8 *(Expert consensus)*
In patients with low adherence, IV formulation should be preferred.

Triple immunosuppression that includes a CNI should be preferably used in patients with:

1. Nephrotic range proteinuria (particularly with nephrotic syndrome) and eGFR>45 mL/min/1.73 m^2 [7-9];
2. Patients who cannot tolerate standard-dose MMF, who are ineligible for CYC-based regimens.

Voclosporin should be preferably used, considering it is the only CNI with RCT evidence in the European population (Expert consensus).[7-9]

As VCS is not yet available in Portugal, TAC should be the next preferred option, although CsA can be used in cases of intolerance to TAC. *(Expert consensus)*

Triple immunosuppression that includes OBZ:

As previously discussed, OBZ is not yet available in Portugal as an indication to treat LN. However, in selected cases, the INWG considers that OBZ can be a valuable *"off-label"* option in patients with:

1. Proliferative LN with nephrotic proteinuria or refractory LN (Expert consensus)[9];
2. History of non-adherence; *(Expert consensus)*
3. Extra-renal manifestations with intense and persistent immunological activity; *(Expert consensus)*
4. Increased risk of GC-related adverse events that imply the need of steroid-sparing strategies. *(Expert consensus)*

Specific conditions

In patients with rapidly progressive renal insufficiency and or crescentic GN, although not well studied in RCT, the INWG considers the following:

1. Preferably use CYC base regimen - consider higher dosing (0.5 g-1 g/m^2) according to the NIH regimen (Expert consensus)[7-9];
2. Triple regimen with CYC plus OBZ (or, if unavailable RTX) is a possible option and the INWG considers that in severe cases it could be used to reduce CYC cumulative dose while maintaining its efficacy (in similarity with regimen that combined CYC and RTX to treat ANCA-associated vasculitis), and provide a safer strategy to reduce GC. *(Expert consensus)*

SUBSEQUENT TREATMENT

1. The chosen immunosuppressive regimen chosen should be continued for at least 36 months (MMF should be started post CYC based regimen), with GC weaning to ≤5 mg/day (prednisone-equivalent) by 3-6 months and slowly withdrawn in patients with sustained CRR for more than 12 months[7-9] (Figure 2).
2. Protocol biopsy can be considered in experienced Nephrology Units, with low procedure-related complication rates:
   - At one year in patients with PR (to evaluate histologic activity and adjust therapy)
   - Post three to four years of treatment (to safely withdraw therapy in patients without histological activity) *(Expert consensus)*

Future Perspectives and Research

Despite significant therapeutic advances, major unmet needs persist in the management of lupus nephritis, highlighting the need for ongoing translational and clinical research. Key priorities include:

The development and validation of non-invasive biomarkers to enable early identification of patients at risk of LN, characterize dynamic pathogenic pathways, and provide reliable monitoring of treatment response and histological activity.

Integration of pharmacogenetics and precision medicine approaches to refine therapeutic selection and individualize treatment strategies according to patient-specific biological profiles.

The development of GC-free therapeutic strategies, aiming to minimize treatment-related toxicity while improving short- and long-term renal outcomes.

Evaluation of emerging targeted therapies, with multiple ongoing trials in SLE and LN assessing sequential B-cell targeting strategies (e.g., rituximab followed by belimumab), the use of obinutuzumab within GC-minimization protocols, and novel complement inhibitors (including iptacopan, ravulizumab, and vemircopan) designed to reduce GC exposure and improve CRR rates.[147-150]

In summary, the therapeutic landscape of lupus nephritis is rapidly evolving, shifting from broad immunosuppression toward targeted, personalized, and glucocorticoid-sparing strategies. Advances in biomarker discovery, precision medicine, and novel biologic and complement-directed therapies hold promise for improving disease control while reducing treatment-related toxicity. Future research should prioritize individualized treatment approaches, optimization of long-term outcomes, and equitable access to emerging therapies. Continued collaboration between clinical researchers, multidisciplinary care teams, and regulatory institutions will be essential to translate these advances into meaningful improvements in patient care and prognosis.

Contributorship Statement

Estela Nogueira, Inês Ferreira and Nuno Afonso: Conceptualization, writing and critical revision of the manuscript
Iolanda Godinho, Sofia Correia, Alice Lança, Raquel Vaz, Helena Pinto, Ivo Laranjinha, Teresa Jerónimo and Clara Santos: Writing and critical revision of the manuscript
António Inácio: Critical revision of the manuscript
All authors reviewed and approved the final version for submission and agree to be accountable for all aspects of the work.

Ethical Disclosures

Conflicts of Interest: Estela Nogueira: Occasional consulting and lecturing fees (GSK, CSL Vifor and Otsuka)
Inês Ferreira: Occasional consulting (GSK and CSL Vifor)
Iolanda Godinho: Nothing to disclose.
Sofia Correia: Occasional consulting and lecturing fees (CSL Vifor)
Alice Lança: Nothing to disclose.
Raquel Vaz: Nothing to disclose.
Helena Pinto: Nothing to disclose.
Ivo Laranjinha: Occasional consulting and lecturing fees (CSL Vifor and Novartis)
Teresa Jerónimo: Occasional consulting and lecturing fees (CSL Vifor)
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ANNEX 1

Table 1. Examples of glucocorticoid regimens for lupus nephritis.

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	**Nil or 0.25–0.5 g/day up to 3 days as initial treatment**	**0.25–0.5 g/day up to 3 days often included as initial treatment**	**0.25–0.5 g/day up to 3 days usually included as initial treatment**
Oral prednisone equivalent (/day)			
Week 0–2	**0.8–1.0 mg/kg (max 80 mg)**	**0.6–0.7 mg/kg (max 50 mg)**	**0.5–0.6 mg/kg (max 40 mg)**
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Legend: max, maximum; adapted form KDIGO 2024 guidelines[7]

Table 2. Practical Recommendations for Managing Non-Immune Factors in LN-Associated CKD

Domain	Recommendation	Rationale
Blood Pressure Control	Target <130/80 mmHg using ACE inhibitors or ARBs	Reduces intraglomerular pressure, proteinuria, and CV risk [83-86]
Lipid Management	Statins for dyslipidemia or nephrotic-range proteinuria	Improves endothelial function and lowers CV risk[87-89]
Glycemic Control	Optimize glycemia; consider SGLT2 inhibitors in diabetic LN	Prevents vascular complications; SGLT2i confer cardiorenal benefits [90,91]
Lifestyle Modification	Smoking cessation, weight control, physical activity, sodium restriction	Reduces CV burden and CKD progression; improves efficacy of drugs (e.g. tobacco and HCQ) [87,88,92]
Steroid Minimization	Early tapering and steroid-sparing agents	Lowers risk of hypertension, dyslipidemia, and atherosclerosis [89]
Hydroxychloroquine	Recommended for all SLE patients unless contraindicated	Improves lipid/glucose metabolism and reduces thrombosis [93-94]
ACEi / ARBs	First-line for proteinuria >0.5–1 g/day	Slows CKD progression and reduces fibrosis [86,95]
SGLT2 Inhibitors	Consider in LN with eGFR >30 mL/min/1.73 m² and persistent proteinuria	Emerging evidence of renoprotection and CV benefit [90-91,96-97]
Non-steroidal MR antagonists	Preliminary data in LN show adjunctive nephroprotection (finerenone) for persistent proteinuria despite optimized therapy; Further data are needed.	Potential to reduce proteinuria and fibrosis [98-99]

Legend: ACE: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CKD: chronic kidney disease; CV: cardiovascular, eGFR: estimated glomerular filtration rate; LN: lupus nephritis; MR: mineralocorticoid receptor; SLE: systemic lupus erythematosus; SGLT: sodium-glucose cotransporter

Key Takeaways

- Cardiovascular risk reduction and renoprotective strategies are essential components in the management of patients with LN.
- ACE inhibitors/ARBs remain the cornerstone for proteinuria control in patients with LN.
- SGLT2 inhibitors represent a promising adjunct, even in non-diabetic CKD, particularly in overweight patients.
- Lifestyle interventions and steroid minimization should not be overlooked.

Table 3. Recommendation statements for physical activity in SLE

1. In case of **osteonecrosis or Jaccoud's syndrome, evaluation** by a **specialist** (rheumatologist, orthopaedic or sports medicine) should be performed before starting physical activity (4/C).
2. In case of **outdoor** activity, adapted measures such as **photoprotection** are necessary, and use of **adequate clothing** against cold is recommended if **Raynaud's** phenomenon is present (1b/A)
3. Physical activities at **high risk of trauma** should be performed with **caution** in persons with SLE using **anticoagulants** or **antiaggregant** treatments (5/D)
4. In case of lupus **flare**, **potential contraindication** to physical activity and exercise should be reassessed (5/D)
5. During **articular flares**, we recommend **avoiding involving the inflamed joint**s during physical activity and exercise (5/D)
6. Physical activity is recommended in all persons with SLE after a medical evaluation of contraindications, if deemed necessary (1a/A).
7. The **baseline level of physical activity** should be assessed before starting physical activity, using dedicated questionnaires or the number of steps per day (5/D).
8. Implementation of physical activity should be adapted in terms of frequency and intensity for each individual, taking into account their abilities, preferences and comorbidities with the aim of adherence to and maintenance of physical activity over the long term (1b/A)
9. Unless otherwise indicated, all persons with SLE with inactive disease or mild disease activity should gradually reach WHO recommendations and/or **150–300 min per week** of **moderate intensity** associated with **strengthening activities** at least **2 days per week** (5/D).
10. A **medical evaluation** should be performed before starting exercise in SLE in order to **identify** potential **contraindications** and allow for personalised adaptations following physical abilities, preferences and comorbidities with the aim of adherence to practice over the long term (1b/A)
11. For better personalisation, exercise programmes should be **supervised** by **qualified professionals** (physiotherapists or professionals trained in adapted physical activity) (1b/A)
12. Implementation of exercise should be gradual by **adapting the frequency and intensity** to the individual's capacities and comorbidities (1b/A)
13. Each exercise session should start with a **warm-up** at low to moderate intensity and should end up with a **cooling down** period, including stretching (5/D)
14. Exercise programmes should be performed in **3–5 sessions each week** and include both **aerobic** and **resistance** training exercises (1a/A).
15. Resistance training should be performed for **1–3 sets per exercise** with **8–12 repetition**s using **rest periods of 1–3 min** (1b/A).

Adapted from Recommendations for physical activity and exercise in persons living with systemic lupus erythematosus (SLE): consensus by an international task force.(2)