

Mechanism of Action and Efficacy of Immunosuppressors in Lupus Nephritis

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Abstract: Approximately 70% of the patients with systemic lupus erythematosus will have clinical evidence of kidney damage during their evolution. Patients with impaired renal function at onset and those with recurrent flares have a poor prognosis. Understanding the mechanism of action of immunosuppressants is essential for proper prescription. Steroids inhibit the DNA sequence that promotes the release of inflammatory cytokines. Phosphoramidate mustard, metabolite of cyclophosphamide, cross-link with the DNA, causing the aggregation of an alkyl group, causing cell death. Mycophenolate inhibits inosine monophosphate dehydrogenase, prevents de novo synthesis of guanine, inducing cell arrest in S phase. Azathioprine blocks the synthesis of purines and induces apoptosis. Calcineurin inhibitors prevent the dephosphorylation of NFAT and reduce the production of interleukin 2. Antimalarials alter the enzymatic release of lysosomes by increasing intravesicular pH. The mechanism of action of rituximab is related to complement-dependent cytotoxicity and the elimination of anti-CD20-labeled B cells. Progress in the knowledge and management of low doses of steroids may change the current paradigm and reduce the frequency of related adverse events. Mycophenolate seems to be a better choice than cyclophosphamide for induction, it is also preferred over azathioprine as a maintenance immunosuppressive agent, although azathioprine is preferred in women with a desire for conception, those pregnant, or with low resources. For treatment-resistant cases, tacrolimus, rituximab or belimumab may be effective. Ongoing clinical trials with new drugs offer promising results.

Keywords: systemic lupus erythematosus, lupus nephritis, mechanism of action, therapeutics, clinical pharmacology

Introduction

Lupus nephritis (LN) is a common complication of systemic lupus erythematosus (SLE). Approximately 70% of the patients with SLE will have clinical evidence of kidney damage during their evolution.¹ In autopsies, lupus nephritis is found in more than 95% of the patients with SLE.² However, deposits of immune complexes have been demonstrated in the kidneys of virtually all SLE patients even if the findings by light microscopy are normal.³ Of all SLE patients, 33% had deterioration of renal function or proteinuria at onset.⁴ Patients with proliferative class (III/IV) and membranous (class V) LN have a probability of progression to end-stage renal disease of 20% and 10% at 5 years, respectively.^{5,6} Before 1980 it was the leading cause of death in patients with SLE, since then it is the second cause of death after infections.² Risk factors for LN include lower age at diagnosis, male sex, being Hispanic, Asian or African.⁶

Patients with SLE represent 2% of hemodialysis population. Among these, women, African-Americans, and those younger than 45 years old are the largest

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group in renal replacement therapy,⁷ and they demonstrate a lower survival rate on dialysis than those without the disease.⁸ The treatment improves the patient's quality of life and reduces the number of flares.

In the following review, we aimed to briefly describe the mechanisms of action and the current usefulness of immunosuppressive therapies in proliferative LN.

Materials and Methods

The review was carried out after searching the PubMed database for clinical trials, pharmacokinetic studies, clinical outcomes, international management guidelines, and molecular bases of the mechanism of action of the immunosuppressants used in lupus. Relevant clinical studies from 1986 to 2021 were included. Molecular-based studies from a period no longer than 10 years to date were included. Clinical studies using unapproved drugs or with little evidence for favorable outcomes in lupus nephritis were excluded.

Glucocorticoids

In 1934 researchers at the Mayo Clinic obtained an extract from the adrenal gland they called "cortin".⁹ Since then, the efficacy of the drug in the management of autoimmune diseases was proven to be successful.

Its mechanism of action is complex. It is divided into genomic and non-genomic. Genomic responses are the most important from the immunomodulation point of view and are of two types: Transactivator and transrepressor mechanisms.¹⁰

Glucocorticoids bind to the cytosolic glucocorticoid receptor (cGR), a multiprotein complex composed of heat shock proteins, immunophilins, p23 and kinases of the MAPK system.¹¹ The binding of the multiprotein complex cGR to FKBP52 and dynein is translocated through the nuclear pore complex by an active transport mechanism mediated by alpha and beta importins. Within the nucleus, glucocorticoids interact with glucocorticoid response elements (GREs).^{10,12}

Transactivation refers to the transcriptional activation of GREs, whereas transrepression relates to the interference of its pro-inflammatory activity. The primary transcription factors modulated by glucocorticoids include the activator protein 1 (AP-1), the nuclear factor kappa B, and interferon regulatory factor 3.^{13,14}

In LN, high doses of methylprednisolone (0.5 to 1 g intravenously) before cytotoxic or antimetabolite are usually given in induction therapy, followed by oral

prednisone (0.5 to 1 mg/kg/day), with dose reduction in a period of 3 to 6 months.

The use of glucocorticoids alone is associated with a 40% probability of doubling serum creatinine at 3 years compared to the combined use of steroid and cytotoxic therapy in proliferative LN.^{15,16}

Doses greater than 7.5 mg per day for more than 3 months are associated with a high rate of adverse events such as bone demineralization, systemic hypertension, edema, weight gain, acne, atherosclerosis, and severe infections.^{11,17} The duration of glucocorticoid therapy is variable, approximately 70% of the patients will continue with prednisone after induction therapy.¹⁸

Due to the high rate of adverse effects, the efficacy of steroid-free treatment has been studied. Fischer et al evaluated 40 patients with class IV LN, receiving induction therapy with CYC. Prednisone was offered only if the extrarenal activity was reported. At 2 years, complete response was achieved in 62.5% of the patients, whereas partial response was achieved in 20%. Among patients who received prednisone <20mg/day or >20mg/day, there was no difference in renal response or flares ($p = 0.58$).¹⁹

The MYLUPUS trial²⁰ compared the efficacy of reduced-dose oral steroid to standard-dose oral steroid. All patients received three 500 mg methylprednisolone pulses plus mycophenolate acid, then randomized to either standard-dose oral steroid (1 mg/kg/d) or reduced-dose steroid scheme (0.5 mg/kg/d). Complete response at week 24, the primary endpoint, was achieved in 19.8% of the patients (19.0% standard-dose, 20.5% reduced-dose; $p = 0.098$). Infections were reported in 57.1% and 35.9% of standard- and reduced-dose steroid patients, respectively ($p = 0.056$), with herpes zoster in 16.7% and 0% ($p = 0.012$).

The RITUXILUP trial evaluated 50 patients treated with 500 mg of Rituximab (RTX) and 1 g of methylprednisolone at day 1 and 15, without prednisone. A combined response, either partial or complete, was achieved in 90% of the patients on an average of 37 weeks. Complete response was maintained in 52% and partial response in 34% of the patients at week 52.²¹

Another study reported the efficacy of treatment with monthly IV cyclophosphamide (CYC) and fortnightly RTX, free of oral steroid, getting a significant reduction of proteinuria, stable renal function, and no evidence of extrarenal activity.²²

In the AURA-LV trial²³ evaluating the efficacy of voclosporin plus mycophenolate and oral steroids (see below), patients were treated with two 0.25–0.5

g methylprednisolone pulses, followed by a fixed 20–25 mg/d starting oral prednisone rapidly tapered to 5 mg/d by 12 weeks, and 2.5 mg/d by week 16. At 12 months, complete and total renal response rates comparing multi-target treatment and control group were 49 vs 24%, and 67 vs 48%, respectively.

Ruiz Irastorza et al evaluated the effect of low-dose (mean 9 mg/day) compared to standard-dose (mean 25 mg/day) of prednisone in 45 patients, obtaining a partial or complete response, at 87% vs 63%, respectively ($p = 0.05$), but with higher rates of adverse events with the standard-dose (67% vs 7%, $p < 0.0001$).²⁴ An average prednisone dose of 7.5 mg/day has been found to be an independent predictor of systemic damage and increased adverse events.²⁵

Currently, different guidelines recommend a “maintenance dose” of ≤ 7.5 mg of prednisone per day.^{26–30} However, the studies mentioned above may open the paradigm of chronic use of steroid in the treatment of LN. Steroid-free or low-dose therapies may have acceptable results with a reduced rate of adverse events.^{31–34}

Cyclophosphamide

CYC is a nitrogen mustard pro-drug that requires oxidation by the cytochrome P450 (CYP) system. Isoforms CYP3A5 and CYP2B6 produce phosphoramidate mustard, which cross-link with the DNA, causing the following effects: first, the aggregation of an alkyl group to guanine on the nitrogen 7 of the imidazole ring; second, forming covalent bonds and causing the rupture of DNA double-strand; and third, inhibition of DNA replication leading to cell death. These effects occur in both active and quiescent lymphocytes.³⁵ The half-life of CYC is 3–12 hours. The further metabolite, acrolein, can provoke hemorrhagic cystitis. CYC inactivation is mediated through the conjugation to 4-glutathionyl-CYC by glutathione S transferases (GSTs).

Oral or intravenous administration results in the same plasma concentration, which correlates poorly with efficacy or toxicity.³⁶ The kidneys excrete 20% of the non-metabolized drug and all metabolites. Therefore, a 25% dose reduction is suggested when the estimated glomerular filtration rate (eGFR) is between 25 and 50 mL/min and 30–50% when the eGFR is < 25 mL/min. In hemodialysis patients, no dose reduction is required, as 22% of the drug is eliminated during a 3-hour session.³⁷

The cumulative dose, oral or intravenous, appears to determine the initial response to CYC treatment, although there may be increased toxicity with the enteral route.^{38,39}

Adverse effects include infections, increased frequency of neoplasms (especially non-Hodgkin's lymphoma and cervical intraepithelial neoplasia), and gonadal toxicity. Ioannidis et al found that 31% of the patients who received CYC pulses had sustained amenorrhea. The dose at which 50% of women developed amenorrhea was 8 g/m^2 , and the treatment at which 90% developed it was 12 g/m^2 .⁴⁰ Interestingly, women with amenorrhea have fewer severe flares than those who menstruate.⁴¹ It has been reported that patients who are homozygous or heterozygous for CYP2C19*2 have a lower risk of developing ovarian failure.^{42,43}

Van Casteren et al evaluated 248 men treated with CYC for cancer, 70% of those receiving $< 7.5 \text{ g/m}^2$ regained fertility, whereas only 10% did so if the dose was $> 7.5 \text{ g/m}^2$.⁴⁴

Its use in LN is widely accepted. Reports from the 1970s provided evidence of its efficacy.⁴⁵ However, it was not until the study by Austin et al published in 1986, became definitive. They compared the effect of five treatment lines, including quarterly intravenous CYC administration. Renal function was better preserved in those receiving cytotoxic therapy, but the statistical significance was only better in the group receiving the intravenous CYC + steroid combination ($p = 0.027$ vs high prednisone monotherapy).⁴⁶

A subsequent clinical trial corroborated the results, further demonstrating that six monthly administration of IV CYC ($0.5\text{--}1.0 \text{ g/m}^2$) then quarterly for 2 years reduced the likelihood of exacerbations compared to those receiving CYC only for the first 6 months. Such treatment is referred to as National Institute of Health (NIH) protocol.¹⁵

In the mid-1990s, the Euro-Lupus Nephritis Trial (ELNT) was developed, with the hypothesis of obtaining the same efficacy with fewer adverse events. The ELNT protocol consisted in the administration of a low fixed dose of 0.5 g of IV CYC given every 2 weeks for a cumulative dose of 3 g. Ninety patients were randomized to one of two groups: NIH or ELNT protocol. Both groups received methylprednisolone 750 mg/day for 3 days and prednisone 0.5 mg/kg/day for 4 weeks with dose reduction, followed by azathioprine as a remission maintenance agent. At 1 year, no differences were found in complete remission, renal flares, or frequency of severe infections.⁴⁷

At 10 years, no differences were found regarding survival (92% in both groups), doubling of serum creatinine, and end-stage renal disease; however, severe infections, hematological and gonadal toxicity were less frequent in the low-dose CYC group.⁴⁸

Patients homozygous for CYP2B6*5 or CYP2C19*2 have a higher probability of progressing to terminal nephropathy, doubling serum creatinine, and a lower likelihood of reaching a complete renal response.⁴² GSTA1 polymorphism could lead to an increased risk of drug resistance, increase in adverse events and a higher risk of CYC unresponsiveness.⁴⁹

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), a fermentation product of *Penicillium brevicompactum* and related fungi, has an inhibitory effect on the nucleic acids synthesis, an effect known more than 50 years ago. It is a selective, reversible and non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), especially type II isoform which is expressed in activated B and T lymphocytes,⁵⁰ limiting the de novo synthesis of guanine, preventing its incorporation into DNA, inducing cell arrest in phase S.

During its metabolism, it is extensively hydrolyzed in mycophenolic acid, the bioactive metabolite. Biotransformation is regulated by the cytochrome system: CYP3A4, CYP3A5, and CYP2C8.⁵⁰

Patients with proteinuria more significant than 1 g/day had lower plasma concentrations and a reduced area on the concentration–time curve (AUC 0–12), compared with patients with proteinuria less than 1 g/day. Similarly, patients with serum albumin <4 g/dL present increased clearance of the drug.^{51,52}

Adverse events occur in more than 50% of the patients; diarrhea is the most common symptom although it is usually mild; 25% of the patients require suspension of the drug. The most common infections are urinary tract infections (10%) and pneumonia (2%), which usually do not require hospitalization.^{53,54}

Its use in LN is widespread, due to its proven efficacy as induction and remission maintenance agent, with good tolerability, enteral administration, and low gonadal impact, although its main disadvantage is cost.

In 2000, Chan et al compared MMF with CYC for induction therapy in 42 patients with proliferative LN. Patients in the MMF group achieved remission in 81% vs 76% in the CYC group (with no statistical significance), and a similar rate of adverse events.⁵⁵ Other studies with

a relatively small number of patients had similar results.^{56,57}

The ALMS, a controlled, randomized, multicenter study compared MMF with CYC in 370 patients. The combined response, complete or partial, was presented in 56.2% of the patients in the MMF group vs 53% in the CYC group.⁵⁴

Most systematic reviews support the use of MMF over CYC,^{58–60} although there are studies that favor the use of CYC,⁶¹ particularly in severe LN, a point to emphasize, since patients with serum creatinine greater than 2.5 mg/dl are typically excluded from the comparative studies.⁶² In the post-hoc analysis of ALMS, it was found that patients with eGFR less than 30 mL/min, MMF had the same response compared to CYC (20% vs 16%, $p = 0.9$), although weekly recovery of renal function was faster with MMF compared to CYC (1.5 mL/min/week, 95% CI 0.99 to 2.02, $p < 0.001$) with no difference in adverse events.⁶³ It is important to remark that in class V LN, MMF and CYC are effective in induction therapy.⁶⁴

MMF is also using a remission maintenance agent.^{58,65,66} The ALMS group also demonstrated during the 36-month follow-up that MMF is superior to azathioprine in terms of therapeutic failure (mortality, requirement for renal replacement therapy, doubling serum creatinine, renal flare, or rescue therapy), observed in 16.4% of the MMF group compared to 32.4% in the AZA group.⁵³

The dual utility of MMF in induction and maintenance therapy may be associated with down-regulation of plasmablasts and plasma cells, with reduced production of immunoglobulins M, A, G and light chains, predominant in the first weeks of initiating therapy, reflecting the modulation of the immune response on short and long-term; those cellular effects were not detected with CYC.⁶⁷

The ALMS study also demonstrated that MMF was the best choice for remission induction in Hispanic patients.⁵⁴ In a retrospective comparative cohort, which included 165 Hispanic patients with ISN/RPS class III, IV or V LN, MMF was superior to CYC and AZA regarding complete renal response and relapse-free disease. No differences were detected between the groups progressing to end-stage renal disease.⁶⁸

MMF is also part of the multitarget protocol as will be seen later in the review. Interestingly, Dall'Era et al in a propensity score methodology, analyzed the ALMS and AURA-LV trials, and concluded that doses of MMF below the recommended target of 2–3 g/d, especially in induction phase, can be effective (1.9 g/day [AURA-LV] vs 2.6 g/

day [ALMS] MMF; mean difference: -0.76 ; 95% CI -0.96 to -0.57 , $p < 0.0001$),⁶⁹ although the clinical relevance should be demonstrated in a randomized clinical trial.

Some authors suggest monitoring MMF concentrations to confirm correct dosing, indicating levels greater than 13 mg/dL 1-hour post-dose,⁷⁰ while others recommend a threshold of 3 mg/L.⁷¹

In a very interesting analysis, Hap et al evaluated serum concentrations of mycophenolic acid (MPA) hourly from 1 to 12 hours post-exposure (C1-C12) in 88 stable patients on maintenance treatment; single nucleotide polymorphisms were also evaluated (ABCC2, OATPs and UGT). C1, C2 and C12 concentrations correlated well with AUC_{0-12} . However, only C12 was associated with infection, anemia and renal flare. The SNP ABCC2, rs2273697 A/G was associated with lower exposure to MPA.⁷²

Luszczynska et al reported that the monitoring of the pre-dose total concentration of MPA shows a correlation, although discrete, with AUC_{0-12} ($r = 0.57$), while the monitoring of the concentration of free MPA is more useful in hypoalbuminaemic patients.⁷³

Alexander et al also detected that patients with albumin >3.5 mg/L reached therapeutic concentrations ($AUC >30$ mg/h/L) with greater probability than hypoalbuminaemic patients.⁷⁴ In this study, the initial empirical dose of MPA in the induction treatment was 30 mg/kg and only 61.8% reached the mentioned therapeutic concentration. The initial mean dose was 1.5 g/day and changed to 2 g/day after measurement. With an $AUC > 30$ mg/h/L, a greater renal response was achieved at 1 year (79.4%).

Both Alexander et al and Pourafshar et al found no association between minimum concentrations (C0) and AUC. In this last study, a weak association between C0 and AUC was detected, since they explained only 30% of the variability of the minimum concentrations of MPA. Therefore, they suggest that the best method is the evaluation of AUC_{0-4} for dose monitoring.⁷⁵ Concomitant use of ACEi/ARB increased C0 and AUC_{0-4} concentrations, while prednisone, diuretics, or hydroxychloroquine did not.

In Japan, an analysis was performed in 10 patients with class III/IV LN, in whom induction treatment with MMF 2 g/day was started and AUC_{0-12} was evaluated early (week 4) and intermediate (week 12) with the objective of evaluating the complete renal response (UPCR <0.5 mg/g and eGFR variation $<10\%$ with respect to baseline) at week 12. All patients with $AUC_{0-12} > 40$ mg/h/L and 33%

of the patients with $AUC_{0-12} < 40$ mg/h/L in the early evaluation (week 4) had a complete renal response, no association detected with the evaluation intermediate of AUC_{0-12} . In the histological evaluation, there were no differences between the activity and chronicity indices between both groups ($p = 0.77$ and 0.48 , respectively).⁷⁶ However, the small number of patients does not allow generalization of the results.

In summary, the routine use of MMF concentrations is not currently recommended, but with the new evidence it would be possible to guarantee personalized management of patients with a moderate-to-severe degree of the disease.

Azathioprine

Azathioprine, synthesized in 1957, is an imidazole derivative, a prodrug metabolized by a non-enzymatic process to mercaptopurine and via glutathione transferase to 6-thioinosinic acid. The liver and erythrocytes eliminate both metabolites. There are two pathways of inactivation of 6-mercaptopurine: first, methylation catalyzed by the enzyme thiopurine methyltransferase (TPMT), which produces the inactive metabolite methyl-6-mercaptopurine;³⁵ second, oxidation catalyzed by xanthine oxidase, from which 6-thiopuric acid is generated, this is why patients receiving allopurinol require dose reduction.⁷⁷ Other metabolites include methyl monophosphate-thioinosine, which is incorporated into DNA, blocks replication and purine synthesis, and thioguanosine triphosphate that blocks RNA and induce apoptosis via Bcl signaling. Due to these characteristics, its effect is more intense in lymphocytes in replication.

Adverse events occur in more than 75% of the patients, requiring dose reduction in 40% of the cases. However, severe infections requiring hospitalization only occur in 9.5%. The main adverse effects are gastrointestinal, mild infections and cytopenias (thrombocytopenia and leucopenia).^{53,78,79}

The severity of symptoms is associated with the genetic polymorphism of TPMT,⁸⁰ especially with three variants: TPMT*2, TPMT*3A, TPMT*3B, and TPMT*3C.^{81,82} These polymorphisms are present in 10% of Caucasian, and whose homozygous defect is present in less than 1%.^{83,84}

The advantage of this drug is its low cost, good tolerability and it is the recommended drug during pregnancy.⁸⁵

The MAINTAIN study, a clinical trial conducted in 27 European centers, included 105 patients with class III, IV,

Vc, or Vd LN from the WHO classification who received induction of remission with fortnightly CYC for 3 months and Maintenance therapy with AZA (target dose: 2mg/kg/d) or MMF (target dose: 2g/d) at week 12. Although renal flares were less frequent with MMF, no statistical significance was reached. Proteinuria, serum creatinine, serum levels of complement C3, hemoglobin and activity scores were similar in the two treatment groups.⁸⁶ At 10 years, renal flares did not differ between groups; death and end-stage renal disease were rare events.⁷⁹ This study shows that, in the Caucasian population, MMF is not superior to AZA in long-term outcomes in maintenance therapy.

Therefore, although MMF appears to be more effective than AZA in preventing renal relapse, the data are not entirely conclusive. In a systematic review, Tian et al estimated the probability of 2-year renal failure: 6% with MMF and 12% with AZA; however, after applying a skeptical prior in the Bayesian analysis, no benefit of one treatment over another was detected.⁸⁷

From an economic vision, in the short term, AZA appears to be of great value compared with MMF; however, in long-term perspective, MMF seems to be cost-effective compared with AZA.⁸⁸

Calcineurin Inhibitors

Although cyclosporine A (CsA) and tacrolimus (TAC) differ in their molecular structure and intracellular binding characteristics, their immunosuppressive properties result from the inhibition of calcium-calmodulin-calcineurin interaction.⁸⁹ CsA binds to cyclophilin while TAC binds to FKBP12 (formerly FK506), thereby preventing dephosphorylation and translocation of nuclear factor of activated T-cell (NFAT), a relevant step in the synthesis of interleukin 2, a cytokine known for promoting T-cell proliferation.⁹⁰ Because calcineurin is involved in the process of vesicle fusion to the mast cell membrane, calcineurin inhibitors reduce the degranulation of these cells⁹¹ and inhibit the expression of chemokines in their surface.⁹²

Metabolism occurs via CYP3A4 and CYP3A5 in the liver, and at the intestinal level by CYP3A4 and P-glycoprotein (P-gp). They have variable oral bioavailability (10–60%), so there is an extensive list of pharmacological interactions.⁹³ Drugs that increase the bioavailability of CNIs include nondihydropyridine calcium antagonists, azole antifungals, and macrolides; on the other hand, drugs that may reduce their bioavailability include rifampicin, isoniazid, phenytoin, carbamazepine, and trimethoprim/sulfamethoxazole.⁹³

Cytochrome P450 polymorphisms produce individual variations that require dose adjustment because of their association with changes in serum drug levels and increased risk of nephrotoxicity.⁹⁴

ICNs are beneficial drugs with broad efficacy in post-transplant renal patients. Its use has been extended in patients with LN, especially tacrolimus, but also cyclosporine.⁹⁵

Bao et al evaluated the efficacy of multitarget therapy (tacrolimus, mycophenolate, and prednisone) in 40 patients with class IV + V LN, compared to intravenous CYC, finding remission at 6 months in 50% versus 5%, respectively. Partial response was present in 40% in both groups.⁹⁶ Another controlled clinical trial comparing multitarget vs CYC therapy in induction therapy showed that after 24 weeks, 45.9% of the patients achieved complete remission, compared to 25.6% of the patients on CYC therapy ($p < 0.001$).⁹⁷

In a fascinating study conducted in Japan, multitarget therapy associated with six monthly pulses of CYC was associated with complete remission in 80% of the patients.⁹⁸

The efficacy of this drug has been corroborated in other studies, most in Asia.^{99–103}

Multitarget therapy as maintenance in the LN has also been shown to be superior to azathioprine in renal relapse rates and adverse events.¹⁰⁴

A good response has been reported in patients with mycophenolate resistance when TAC is added to management, with partial or complete remission reported from 50% to 70% of the patients and reduction in requirements of corticosteroids.^{105–107} Combined administration with MMF and CsA also have reported success.¹⁰⁸

The hypothesis related to the response obtained in refractory cases is related to the overexpression of P-gp in CD4+ T lymphocytes associated with MDR-1 gene polymorphisms in some patients with lupus;^{109,110} the main function of P-gp is the extrusion of some drugs from the cell membrane. The persistent expression of P-gp can induce resistance to steroids compared with those with reduced expression and function.^{111,112} ICNs are inhibitors of P-gp increasing the sensitivity to other immunosuppressants, particularly steroids, reversing drug resistance.¹¹³

The most frequent complication with these agents is infection, reported in up to 33% of the patients, but requiring hospitalization only 6% of them.¹⁰⁶ A high incidence of cytomegalovirus and herpes zoster infection has been

reported.^{101,114} Other complications include diarrhea (12%), dyspepsia (6%), and transient rise in serum creatinine (6%), which usually do not require discontinuation of therapy. Serum levels of TAC in the studies are generally between 5 and 8 ng/mL.

An analysis of several controlled clinical trials, TAC proved to be the drug with the highest clinical remission rate, as well as the one with the lowest probability of severe infections compared to MMF, AZA and CYC.^{17,115,116} Therefore, TAC is a good option especially combined with MMF and appears to be superior to achieve remission rates compared to IV CYC.¹¹⁷ However, most studies have been conducted in Asian patients, so high-quality multi-ethnic clinical trials are required to test its efficacy in different populations.¹¹⁸

Voclosporin is a new generation calcineurin inhibitor, with a structure derived from cyclosporin A, its stereoisomer Z-ISA247 binds to cyclophilin A. The higher affinity of voclosporin is explained by van der Waals forces between its only side chain and cyclophilin A. This drug shows greater immunosuppressive activity compared to CsA in vitro and in vivo, in animal models of autoimmunity and transplantation.¹¹⁹ In an animal model study with non-human primates, individuals with normal renal function have prescribed a dose of 0.4 mg/kg (administered with gelatin capsules orally) on day 1 and 0.4 mg/kg thereafter every third day until the morning of the 10th. Individuals with severe renal failure were prescribed a single dose of 0.4 ng/kg on day 1. The maximum concentration on day 1 was 122 ± 45 ng/mL and with severe renal failure, 147 ± 50 ng/mL, this concentration varies, even more, 10 days after administration, with 142 ± 53 ng/mL, for individuals with normal renal function (urinary excretion in 24 hours [Eu-24] of 107.3 ± 29.9 μ g) and of 184 ng/mL for individuals with severe renal failure (Eu-24 of 52.8 ± 18.6 μ g), despite the difference in the administered dose.¹²⁰

The use of voclosporin in lupus nephritis was carried out in the AURA-LV trial, a multicenter, double-blind, placebo-controlled study to evaluate the usefulness of voclosporin plus the standard of care, MMF, or corticosteroids. In this study, 265 individuals from 20 countries in America, Europe, and Asia were included, 88 individuals were assigned to the placebo group, 89 assigned to low dose VCS (23.7 mg BID), and 88 assigned to high dose VCS (39.5 mg BID), all groups also received standard treatment with MMF 2 g/d plus oral corticosteroids. Complete renal remission (CRR) was achieved in 32.6%

of the individuals in the low dose VCS group (OR = 2.03; 95% CI: 1.01–4.05; $p = 0.046$) and in 27.3% of the individuals with high doses of VCS (OR = 1.59; 95% CI: 0.78–3.27; $p = 0.204$), compared with 19.3% of the placebo group. VCS doses were superior to placebo for CRR at 48 weeks. Furthermore, the individuals showed a significant change in the decrease in urine protein-to-creatinine ratio (UPCR) and increase in serum albumin. At week 48, anti-dsDNA antibodies decreased 7% in the placebo group, 51% in the low-dose VCS group, and 38% in the high-dose VCS group. The SLE activity presented differences between the groups, at 48 weeks 53.4% of the patients in the placebo group still had SELENA-SLEDAI scores >6, compared with 29.2% and 40.9% in the group of SCV at low and high doses, respectively. Adverse effects reported at week 24 increased in individuals with low doses of VCS (28.1%), compared with high doses (25.0%) and placebo (15.9%); the most frequent adverse effect in all groups was infections. This study further demonstrated that the use of VCS in patients with lupus nephritis maintains a significantly higher proportion of CRR at 48 weeks of treatment compared to placebo.²³

Finally, AURORA trial (NCT03021499) was a 52-week Phase III global, double-blind, placebo-controlled study to evaluate whether VCS when added to background therapy of MMF can increase speed of and overall renal response rates in the presence of low-dose steroids. A total of 357 patients with active LN were enrolled in this study across sites in 27 countries. AURORA met its primary endpoint, achieving statistically superior renal response rates (UPCR of ≤ 0.5 mg/mg, eGFR ≥ 60 mL/min, or no confirmed decrease from baseline in eGFR of >20%) of 40.8% for intervention (voclosporin 23.7 mg BID plus MMF 2 g/day) vs 22.5% for the control (placebo plus MMF 2 g/day) (OR = 2.65, 95% CI; $p < 0.001$). Recently, the US Food and Drug Administration had approved Voclosporin for the treatment of adult patients with active lupus nephritis. Voclosporin significantly demonstrated improvement in renal response rates in AURORA Phase 3 study and the AURA-LV trials. And it is now commercially available in the US.

Tables 1 and 2 summarize the main studies to date for induction and maintenance therapies in lupus nephritis.

Antimalarials

It is important to note that 40% to 50% of the patients will not respond to induction, 38% will have flares in the course of the disease, and 20% to 30% will progress to end-stage renal disease,⁵ so the best treatment is one that

Table I Main Randomized Clinical Trials in Induction to Remission

Study	Patients (Women)	Lupus Nephritis Classification ^a	Average Cr or GFR	Average Proteinuria	Scheme (Patients)	Follow-Up	Results
ELNT ^{47,48}	90 (93%). White: 76. Black: 8. Asian: 6.	OMS. III: 21 IV: 62 Vc/Vd: 7	1.1 mg/dl	3 g/day	0.5g IV every 15 days for 3 months vs CYC 0.5–1 g/m ² monthly for 6 months	10 years	Therapeutic failure: 16% (low-dose) vs 20% (high-dose); kidney disease: 27% (low-dose) vs 29% (high-dose); end-stage renal disease: 5% (low-dose) vs 9% (high-dose). (p>0.05)
Ginzler et al ¹⁶⁸	140 (90%). White: 17%. Black: 56%. Asian: 8%. Hispanic: 19%.	OMS III: 15%. IV: 55%. V: 20%. Mixed: 10%.	1.0 mg/dl	4.2 g/day	CYC 0.5–1 g/m ² monthly for 6 months vs MMF 3 g/day	6 months	Complete response: 22.5% (MMF) vs 5.8% (CYC) (p=0.005). Partial response: 29.6% (MMF) vs 24.6% (CYC) (p=0.051)
ALMS ⁵⁴	370 (84.6%). White: 39%. Black: 33%. Other: 72% (Hispanic approx. 10%).	ISN/RPS III or III + V: 15.7% IV or IV + V: 68.1% V: 16.2%	1.1 mg/dl	4.1 g/day	CYC 0.5–1 g/m ² monthly for 6 months vs MMF 3g/day	6 months.	Complete/partial response: 56.2% vs 53% (p>0.05). Black and Hispanic ethnicity show a better response.
ALMS sub-analysis ⁶³	32 (86%). White: 51%. Asian: 26%. Other: 23%.	ISN/RPS III or III + V: 17.5% IV or IV + V: 82.5%	GFR: 24 mL/min	4.3 g/day	CYC 0.5–1 g/m ² monthly for months vs MMF 3g/day	24 weeks	Response: 20% (MMF) vs 16.7% (CYC) (HR 1.2, p=0.9). Recovery GFR: 1.51 mL/min/week. Faster with MMF (p<0.001).
AURA-LV ²³	230 (86.8%). White: 40.8% Black: 5.3% Asian-Indian: 22.6% Asian: 27.2% Other: 4.2%	ISN/RPS V: 14.7% III or IV: 67% III + V or IV + V: 18.1%	GFR: 99.8 mL/min	Urine protein-to-creatinine ratio: 4.69 g/g	Voclosporin low dose: 23.7 mg BID + MMF 2 g/d + corticosteroids or high dose: 39.5 mg BID + MMF 2 g/d + corticosteroids vs placebo + MMF 2 g/d + corticosteroids	24 weeks	CRR: low dose 32.6% (OR = 2.03, p = 0.046), high dose: 27.3% (OR = 1.59, p = 0.204) vs placebo: 19.3%
Furie et al ¹⁶⁵	393 (88%) Asian: 50% White: 33% Black: 14% Other: 3%	ISN/RPS III or IV: 58% III + V or IV + V: 26% V: 16%	GFR: 100.5 mL/min	Urine protein-to-creatinine ratio: 3.4 g/g	Belimumab 10 mg/kg at day 1, 15, 29 and every 28 days to week 100 vs placebo	104 weeks	Primary efficacy renal response: Belimumab 43% vs placebo 32% (OR 1.6, p= 0.03)

Notes: ^aHistopathological classification of the World Health Organization (WHO). International Society of Nephrology/Society of Nephrologists (ISN/RPS).

Abbreviations: Cr, creatinine; GFR, glomerular filtration rate; CYC, cyclophosphamide; MMF, mycophenolate mofetil.

Table 2 Main Randomized Clinical Trials in Maintenance of Remission

Study	Patients (Women)	Lupus Nephritis Classification ^a	Average Creatinine	Average Proteinuria	Induction to Remission	Maintenance Dose (Patients)	Results
MAINTAIN ⁸⁶	105 (91%). White: 79%. Black: 12%. Asian: 9%.	OMS. III: 31% IV: 58% Vc: 3%. Vd: 8%	1.0 mg/dL	2.94 g/day (AZA) 3.63 g/day (MMF)	CYC 0.5g IV every 15 days for 3 months.	AZA 2mg/kg/day. Vs MMF 2g/day.	Kidney disease: 19% (MMF) vs 25% (AZA) (HR: 0.75, p=0.48).
ALMS ⁵³	227 (86%). White: 44%. Black: 10%. Asian: 33% Hispanic: 13%	ISN/RPS. III o IV + V: 13%. IV o IV + V: 72% V: 15%	0.86 mg/dL	0.82 g/day (AZA) 0.90 g/day (MMF)	CYC 0.5 a 1 g/m ² monthly for 6 cycles vs MMF 3 g/day.	AZA 2 mg/kg/day. vs MMF 2g/day.	Treatment failure 16.4% (MMF) vs 32.4% (AZA). (HR:0.44, p=0.003).

Notes: ^aHistopathological classification of the World Health Organization (WHO). International Society of Nephrology/Society of Nephrologists (ISN/RPS).

Abbreviations: MMF, mycophenolate mofetil; AZA, azathioprine; CYC, cyclophosphamide.

prevents the development of flares. Among them, antimalarials are drugs of proven efficacy.

Hydroxychloroquine (HCQ) and chloroquine (CQ) are 4-aminoquinolines. They are well absorbed, with 80% bioavailability after oral administration and half-life of 40 days.¹²¹ They have hepatic metabolism and renal excretion. The onset of its anti-inflammatory effect takes between 4 and 6 weeks, while the time to reach stable concentrations in blood is estimated between 4 and 6 months.¹²²

These agents can suppress the antigen presentation, inhibit the synthesis of prostaglandins, cytokines, and influence both Toll-like receptor signaling and lymphocyte differentiation,^{123–125} as well as improving the Treg cell balance,¹²⁶ with other proven pleiotropic effects that include improving proteinuria^{127,128} and reduce accelerated atherosclerosis frequent in patients with SLE.¹²⁹

The relationship of pro- and anti-inflammatory serum cytokines in lupus has been evaluated; a reduced IL-10/TNF-alpha ratio could be related to a reduction in the percentage of CD4+ CD25+ regulatory cells (Treg). Antimalarials appear to be especially beneficial in patients with this inflammatory profile.^{130,131}

Due to the lipophilic and lysomotropic nature of the HCQ, it can easily cross through the cell membrane. In the cytoplasm, the free base accumulates within the lysosomes; these have high acid content generated by the activity of the hydrogen ATPase-V. High concentrations of HCQ raise the lysosomal pH, from 4.7 to 6. The

intralysosomal alkalization results in its expansion and vacuolation, interfering with the enzymatic release, receptor recycling, and repair of its membrane.¹³²

Antimalarials are inhibitors of P-gp, so they have the potential to reduce drug resistance of autoreactive T lymphocytes.¹³³

An additional benefit is that these therapeutic agents can be used during pregnancy.⁸⁵

At recommended doses, the toxicity is up to 2% after 10 years of treatment, and up to 20% after 20 years of treatment.¹³⁴ The exact mechanism by which antimalarial drugs cause retinal toxicity is not well elucidated, however studies in animal models suggest that the damage in lysosomal function produces an accumulation of lipofuscin,¹³⁵ which is toxic to photoreceptors and retinal pigment epithelium cells (RPE), where HCQ is deposited 20,000 times above blood levels.¹³⁶ Seven percent of the patients with CQ and 0.6% of the patients with HCQ will have corneal deposits. Other adverse effects are headaches (12%), gastrointestinal disturbances (15%) and ototoxicity (0.5%).

Current recommendations advise testing within the first 6 months of treatment and annually if there are clinical findings suggestive of imminent toxicity (major risk factors), or yearly after 5 years of continuous therapy.¹³⁴ Unfortunately, there is poor adherence to the recommendations, less than 20% of the clinicians are aware of ophthalmologic assessment recommended by the clinical guidelines.¹³⁶

The major risk factors for retinal toxicity: >5 years of use (assuming no other risk factors), high daily doses (>400 mg or 5 mg/kg/day of HCQ and >250 mg or 2.3 mg/kg/day of CQ), concomitant use of tamoxifen, subnormal glomerular filtration rate, and preexisting visual impairment (retinopathy or maculopathy). It is recommended that the dose does not exceed 5 mg/kg/day, taking as reference the ideal weight of the patient.¹³⁴

Different observational studies are described in Table 3.

Rituximab

CD20 is a member of the family of integral membrane proteins, expressed during cell differentiation from pro-B cell to a plasma cell. CD 20 regulates the activation

process of cell cycle and differentiation. In vitro, a role for CD20 as a calcium channel is proposed.¹³⁷ It has been demonstrated that patients with CD20 deficiency exhibit independent T-cell immunodeficiency.¹³⁸ RTX is a murine/human unconjugated chimeric monoclonal antibody, consisting of two heavy chains of 451 amino acids and two light chains of 213 amino acids with a molecular weight of 145 kD. The vector was cloned into Chinese hamster ovary cells as a source of immunoglobulin production.¹³⁹

The Fc portion is responsible for the multiple mechanisms of action related to RTX including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). Many immune cells, including NK, macrophages, and monocytes, eliminate anti-CD20-labeled B cells.^{140,141}

Table 3 Studies Involving the Use of Antimalarials in Systemic Lupus Erythematosus

Study	Patients	Primary Outcome	Results
Tsakonas et al ¹⁶⁹	47. - 25 HCQ - 22 placebo	Flares	Protection against the occurrence of kidney disease (RR = 0.26; 95% CI: 0.03–2.54, p= 0.025).
Fessler et al ¹⁷⁰	518 (34% Hispanic) - 291 with HCQ - 227 without HCQ	Systemic damage accumulation	Reduced risk of accumulated kidney damage (HR = 0.68; 95% CI: 0.53–0.93, p= 0.014).
Ruiz-Irastorza et al ¹⁷¹	232 - 62 HCQ - 46 CQ - 42 HCQ and CQ - 82 without antimalarial	Survival	Increased 15-years cumulative survival in antimalarial users compared to non-users (0.95 vs 0.68, p<0.001).
Sisó et al ¹⁷²	206 - 56 HCQ or CQ prior to the lupic nephropathy diagnosis - 150 controls prior to the lupic nephropathy diagnostic	Systemic complications	Increased creatinine greater than 4 mg/dL: 2% (HCQ or CQ) vs 11% (control) (p=0.029). Terminal nephropathy: 2% (HCQ or CQ) vs 11% (control) (p= 0.044).
Pons-Estel et al ¹⁷³	203 (39% Hispanic) - 161 HCQ - 42 without HCQ	Nephroprotection	Reduced risk of nephropathy in HCQ users (HR = 0.29; 95% CI: 0.13–0.68, p= 0.0043). Cumulative probability of 20% kidney damage within 5 years (HCQ) vs 47% (control) (p<0.001).
Shinjo et al ¹⁷⁴	1480 (Latin American) - 1141 HCQ or CQ - 339 without antimalarial	Mortality	38% reduction in mortality rate (HR = 0.62; 95% CI: 0.39–0.99).
Pons-Estel et al ¹⁷⁵	795. (Latin American) - 265 with nephropathy. - 530 without nephropathy	Nephroprotection	Reduced risk of nephropathy in control group vs clinical cases (OR 0.38; IC 95%: 0.25–0.58).

Abbreviations: HCQ, hydroxychloroquine; CQ, chloroquine.

The half-life is 59.8 hours (ranged from 11.1 to 104.6 hours) after the first infusion and 174 hours (range from 26 to 442 hours) after the fourth infusion. The half-life is increased to 10 to 14 days in patients with renal disease.¹⁴² RTX persists in the circulation for 3 to 6 months and is not eliminated by conventional hemodialysis.¹⁴³

The LUNAR study¹⁴⁴ evaluated 144 patients with class III or IV LN; patients were randomized to receive an intravenous infusion of placebo or 1 g of RTX at 0, 2, 24 and 26 weeks. All patients received three boluses of 1 g methylprednisolone, mycophenolate 1 g three times a day, and prednisone. At week 52, it showed that the incidence of complete or partial response was numerically higher with RTX but without statistical significance. However, there were further reductions in anti-DNA titers and improvements in complement levels with RTX. The frequency of infections and hospitalizations was similar compared to placebo. Therefore, the use of RTX as induction therapy for proliferative varieties was not supported.

However, some experts argue that the positive effect of RTX may have been diluted by the concomitant use of high doses of MMF. Interestingly, the subgroup of Hispanic and African American patients benefited most from therapy.¹⁴⁵ The dose commonly used in LN ranges from 375 mg/m² weekly for 4 weeks to 2 doses of 1 g every 2 weeks.¹⁴⁶

As mentioned, the RITUXILUP trial evaluates the effect of two doses of rituximab, MMF and MTP, without oral prednisone. The response was obtained in almost 90% of the patients: complete remission in 52% and partial remission in 34% at 37 weeks.²¹

Interestingly, Gomez Mendez et al as part of a sub-analysis of LUNAR trial found that the achievement of complete peripheral depletion was statistically associated with renal response, with an odds ratio of 5.8 (95% CI: 1.2–28; $p=0.03$).¹⁴⁷

The most common adverse events of RTX are related to the first application. These include headache, nausea, urticaria, and hyper- or hypotension. These reactions, which rarely appear to be dangerous, may decrease with glucocorticoid premedication.

There is greater susceptibility to acute or late-onset neutropenia, and infections (mainly pneumonia).^{148,149} Low IgG levels (<6 g/L) before RTX can predispose to severe infections, especially in the first 3 months following RTX infusion¹⁵⁰; other risk factors are diabetes, cumulative RTX dose, and the use of AZA.¹⁴⁸ Vaccination with live virus is not recommended after RTX.¹⁴³ A hepatitis

B virus serologic profile before RTX is significant as the virus can reactivate with the monoclonal antibody.¹⁵¹

One of the most severe complications is progressive multifocal leukoencephalopathy (PML), probably caused by reactivation of the JC virus.^{152,153} In one study, the viral prevalence in peripheral blood mononuclear cells, serum, and urine samples was 2.4%, 0%, and 50%, respectively, in the healthy donors, and 26%, 16%, and 86%, respectively, in the patients treated with RTX.¹⁵⁴

Another cause of concern is the development of anti-chimeric antibodies against RTX, although its clinical relevance in SLE patients should be determined.^{155–157}

Belimumab

Belimumab is a monoclonal antibody, an IgG1 λ immunoglobulin directed against BLyS, also known as the B-cell activating factor (BAFF). BAFF is a member of the tumor necrosis factor (TNF) superfamily of cytokines, it binds to three different receptors: the transmembrane activator and calcium-modulator, and cyclophilin ligand interactor (TACI), B cell maturing antigen, and BLyS Receptor type 3 (BR3).¹⁵⁸ Inhibition of BAFF, which is overexpressed in SLE,¹⁵⁹ promotes apoptosis and decreases B cell survival, thus making it an important therapeutic agent. Belimumab has a mean initial volume of distribution of 40–57 mL/kg, a distribution phase half-life of 1–2.2 days, and a terminal elimination half-life of 8.5–14.1 days. Clearance is 7 mL/kg/day after administration of a single dose.¹⁶⁰

The main adverse events are infections; however, the risk remains stable in patients after 7 years of follow-up. Other documented adverse effects are hypersensitivity, headache, nausea, fatigue, and 16% of the patients have psychiatric adverse effects.^{161,162}

Belimumab was evaluated in two phase III clinical trials, comparing belimumab at doses of 1 and 10 mg/kg plus standard therapy and placebo plus standard therapy in patients with SLE and positive autoantibodies. The BLISS-52 trial was conducted in Asia, Europe, and South America with a 52-week follow-up, and BLISS-76 was conducted in North America and Europe with a 76-week follow-up. The administration of the medications was carried out on days 0, 14, and 28 and then every 28 days until 48 weeks. Efficacy at week 52 was evaluated by SRI (SLE Respond Index), defined as a reduction of ≥ 4 points in the SELENA-SLEDAI score. In the belimumab group at 10 mg/kg, there was a better response compared with placebo (43.2% versus 33.5%; $p = 0.017$), the response rate in the 1 mg/kg

belimumab group (40.6%) was also higher than in the placebo group ($p = 0.089$). SRI response rates at 76 weeks were higher in the group of belimumab at 10 mg/kg (38.5%) ($p = 0.13$) and belimumab at 1 mg/kg (39.1%) ($p = 0.11$) compared with placebo (32.4%).^{163,164}

Furie et al¹⁶⁵ conducted a phase III trial in 21 countries in which 228 patients diagnosed with biopsy-proven lupus nephritis received intravenous belimumab at a dose of 10 mg/kg in addition to standard therapy and were compared with 224 patients who received placebo and standard therapy. The response in the improvement of renal function was evaluated with a urinary protein-to-creatinine ratio (UPCR) ≤ 0.7 mg/g, eGFR ($<20\%$ deterioration with respect to baseline creatinine prior to kidney disease), and absence of rescue treatment. At week 104, patients in the belimumab group had a better response in renal function compared to the placebo group (96 of 223 patients [43%] versus 72 of 223 [32%]; OR=1.6; 95% CI: 1.0–2.3; $p = 0.03$). Time to efficacy at 52 weeks was also longer in the belimumab group compared to patients in the placebo group (104 of 223 patients [47%] versus 79 of 223 patients [35%]; OR = 1.6; 95% CI: 1.1–2.4; $p = 0.02$).

Atisha-Fregoso et al¹⁶⁶ enrolled 43 adults with recurrent or refractory LN (Class III, IV alone or in combination with class V) and randomized 1:1 to receive belimumab or placebo after treatment with RTX plus CYC. All patients had been treated with either CYC or MMF in the past. At week 48, a complete or partial renal response occurred in 11 (52%) of 21 patients receiving belimumab, compared to 9 (41%) of 22 patients in the group who did not receive belimumab ($p = 0.452$). Lack of improvement in or worsening of LN was the major reason for treatment failure. B cell depletion occurred in both groups, but the percentage of B cells remained lower in those receiving belimumab ($p = 0.0012$).

Thus, belimumab has been shown to be effective in the induction treatment phase in combination with mycophenolate, reducing the steroid dose and the risk of progression to end-stage chronic kidney disease.¹⁶⁷

Ongoing Clinical Trials

Among others, obinutuzumab, a third-generation type II anti-CD20 antibody, has recently been evaluated as a potential treatment for lupus nephritis. A multicentric trial with obinutuzumab (NOBILITY) has been evaluating the safety and efficacy of this drug in participants who receive obinutuzumab 1000 mg intravenous infusion on Days 1, 15, 168, and 182 along with mycophenolate mofetil or mycophenolic acid. They found that 34% ($p = 0.1145$) of patients achieved

complete renal response, and 55% ($p = 0.0150$) achieved a partial response at week 52 [ClinicalTrials.gov: NCT02550652].

Abatacept is a fusion protein that selectively modulates the molecular interaction between antigen-presenting cells (APC) and T lymphocytes is essential for the optimal activation of the immunological response and requires the participation of two membrane receptors, CD80 and CD86. Recently, 695 participants were enrolled in a trial (ALLURE) comparing Abatacept 30 mg/kg vs placebo. They did not find a significant difference when treating patients with abatacept vs placebo, 35% vs 33.5% ($p = 0.7264$), but those who received abatacept appeared to show more rapid and more sustained proteinuria reduction [ClinicalTrials.gov: NCT01714817].

Ocrelizumab (OCR), a humanized monoclonal antibody directed against the B-cell CD20 cell surface antigen, with immunosuppressive activity has been evaluated in patients who received OCR 400mg, 1000mg or placebo. In this trial (BELONG) 42.7%, 31.5% and 34.7% of the participants achieved a complete renal response at week 48 [ClinicalTrials.gov: NCT00626197].

Limitations

The present review is exhaustive, but it is not feasible to compile information that constantly appears in the medical literature. It is possible that evidence with preliminary reports of effectiveness in lupus nephritis has not been included. However, we believe that the compilation and evaluation of the information available up to the time of publication of this review will provide a well-documented overview in the treatment of lupus nephritis.

Conclusions

Lupus nephritis remains one of the most serious complications of systemic lupus erythematosus, and its early detection is essential to provide the best available treatment. Currently, there are several management alternatives, both in the remission induction phase and in the maintenance phase. Mycophenolate mofetil remains the mainstay of treatment, but cyclophosphamide is a less expensive option and perhaps more effective in severe kidney injury. Rituximab is an option that is still under study, although it is currently reserved for resistant cases. Calcineurin inhibitors are an excellent alternative, especially voclosporin, recently approved by the FDA. Other agents like belimumab offer promising results. Ongoing clinical studies will determine whether immunosuppression options in lupus nephritis are extended.

Acknowledgments

The authors thank Dr Luis Estrada-Loyo, Dr Ernesto Roldan-Valadez and Dr Julio Casasola-Vargas for their support for the literature search and writing style.

Disclosure

The authors of this review declare no conflicts of interest for this work.

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