Rev. Colomb. Nefrol. 2014; 1(2): 101- 114. http//www.revistanefrologia.org

Review article

http//doi.org/10.22265/acnef.1.2.182

Lupus nephropathy

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Abstract

Lupus nephritis (LN) occurs between 30% and 70% of patients with systemic lupus erythematosus (SLE), depending on race and sex. LN appears early in the disease with prevalence of severe forms such as classes III, IV and mixed (V + III IV or V +). 50% of adults and 70% of children with lupus born in Colombia, suffer LN sometime in their lifetime; in this population 25% of children and 38% of adults have nephrotic syndrome. The remission rate at six months is low, the proteinuria in nephrotic range, and the incraease of baseline creatinine predict failure to achieve remission at 6 months.

Key words: Lupus, Nephritis, Nephrotic Syndrome, Proliferative glomerulonephritis.

Nefropatía lúpica

Resumen

La nefritis lúpica (NL) se presenta entre el 30 y 70% de los pacientes con lupus eritematoso sistémico (LES), dependiendo de la raza y el sexo, ocurre temprano en la enfermedad y predominan las formas graves, clases III, IV y mixtas (V + III o V + IV). El 50% de los adultos y 70% de los niños colombianos con lupus sufren NL en algún momento de la vida; en esta población el 25% de los niños y el 38% de los adultos presentan síndrome nefrótico, la tasa de remisión a 6 meses es baja, la proteinuria en rango nefrótico y la elevación de creatinina basal, predicen falla en el logro de remisión a 6 meses.

Palabras clave: Lupus, Nefritis, Síndrome Nefrótico, Glomerulonefritis proliferativas

Introduction

Lupus nephritis (LN) is defined, according to ACR (American College of Rheumatology)[1], its LN[2] guidelines and recommendations EULAR / ERA-EDTA (European League Against Rheumatism and European Renal Association-European Dyalisis and Trasplant Association)[3], such as the presence of persistent proteinuria> 500 mg / 24 hours, or 3+ count in occasional urine sample, or the presence of cell cylinders (haematocytic, granular, tubular or mixed). The SLICC group (Systemic Lupus Erythematosus International Collaboration Clinics) [4] defines it by the presence of proteinuria ≥500 mg / 24 hours or proteinuria / creatinuria (UPCR) ≥50 mg / mmol or erythrocyte cylinders. It states that the presence of renal biopsy compatible with LN plus the presence of antinuclear antibodies (ANA) or antiDNA, are sufficient criteria to classify as a lupus patient.

Received: 17th of October, 2013, Aceptado: 6th of September, 2014

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The frequency of LN varies according to race, sex and age; in the EUROLUPUS[5] cohort, with 1,000 patients, 97% of them caucasian, 16% had LN at the beggining of the disease and 36% during their evolution. Overall, 30% of the patients with LN are white[6] and 60% are African-American[7]. In the GLADEL[8] cohort (Latin American Lupus Study Group, with the acronym in english), 51.7% of the patients presented LN, 58.3% were mestizos and Afro-Latin Americans and 43.6% were white Latin-Americans. Similar proportions are described in the LUMINA[9] cohort (Lupus in Minories Nature or Nurture). In Colombia 50% to 55% of adults[10-12] and 75% of children[13] with systemic lupus erythematosus (SLE) suffer LN at some point in their evolution.

Between 10% and 25% of adults with LN will progress to end-stage cronic kidney disease (CKD) [14,15]. The proliferative forms are the most serious, common and those that most lead to IRCT[16].

In Colombia, there are no prospective studies that determine the percentage of patients with LN who will later develop ESRD, but in several cohorts severe histological forms predominate[10,11,17]. Using the histological classification of the World Health Organization (WHO), in 2 cohorts located at the city of Medellín, a predominance of proliferative forms was found. In a population of 46 patients with LN in the Hospital Universitario San Vicente de Paul11, 46% had LN class IV, 7.8% class III, 9.3% mixed forms (membranoproliferative) and 15.6% class V (pure membranous). In a group of 32 patients with LN at Clinica Leon XIII10, LN class IV represented 50%, Class III 10%, and Class V 19% of the biopsies performed.

According to the classification of the International Society of Nephrology and the Society of Renal Pathology, ISN / RPS, in 140 biopsies performed at the Pablo Tobón Uribe Hospital, we found that 83.87% of cases had proliferative LN (Class IV 63.75 %, Class III 13.42% and mixed forms, V / III or V / IV, 6.7%)[18]; Likewise, in a population selected for severity and resistance to standard immunosuppression, treated with rituximab (RTX), 76% of the patients had proliferative LN[19].

SLE appears to be more severe in children and teenagers; Between 60% and 80% present LN during their evolution, two thirds with histological classes III or IV. Between 10% and 50% reach IRCT[20,21].

Pathological anatomy

Renal biopsy is of great importance in the diagnostic approach of NL[16]; the clinical-pathological correlation is inaccurate[11], so the result of the renal biopsy is a guidance tool to determine the treatment and to provide information about the prognosis[3,22,23]. Additional, it will rule out antiphospholipid syndrome (APS) nephropathy[24,25], thrombotic microangiopathy[26] and primary glomerulopathy.

The instruction to perform renal biopsy vary according to the working groups; ACR2 indicates renal biopsy in patients with SLE who show increased creatinine without alternative causes such as sepsis, hypovolemia or medications; confirmed proteinuria ≥1 gram / 24 hours; or the combination of proteinuria ≥500 mg / 24 hours and cell cylinders; or hematuria ≥ 5 AP erythrocytes. The EULAR / ERA-EDTA3 guidelines suggest renal biopsy in all lupus patients with reproducible proteinuria ≥ 500 mg / 24 hours, especially if they have glomerular hematuria or cellular cylinders.

The consensus of the group of systemic autoimmune diseases (GEAS) of the Spanish Society of Nephrology (SEN) and the Spanish Society of Internal Medicine (SEMI) 23 indicate the renal biopsy in all patients with SLE that present: unexplained deterioration of renal function; Proteinuria confirmed ≥500 mg / 24 hours; UPCR ≥50 mg / mmol in morning sample or in 24-hour period urine; or active urinary sediment. All 3 groups suggest using the ISN / RPS classification of 2003[27] (Table 1).

The ISN / RPS classification seeks to unify concepts and homogenize terms by modifying the WHO classification[28,29]. According to this new classification[27], subendothelial or subepithelial deposits may be demonstrated by electron microscopy or immunofluorescence but not by light microscopy in Class II. Class III and Class IV are subdivided into active (A), chronic (C) and active-chronic (A / C), depending on the characteristics of the histological lesions. In turn, the LN Class IV is subdivided into global (≥50% of the glomeruli involved have global lesions) and

Table 1. Histological classification of lupus nephropathy according to the International Society of Nephrology and the Society of Renal Pathology 2003

Class I: Minimal mesangial nephritis
Normal light microscopy with mesangial deposits in immunohistology and electron microscopy
Class II: Proliferative mesangial nephritis
Broadening and / or mesangial proliferation in light microscopy
Class III: Focal proliferative nephritis (A, A / C, C)
Intracapillary proliferation in less than 50% of the glomeruli, with subendothelial immune deposits
Class IV: Diffuse proliferative nephritis (A, A / C, C)
Intracapillary proliferation in 50% or more of the glomeruli, with subendothelial immune deposits
Case V: Membranous nephritis
Subepithelial immune deposits; Classes II, III or IV may coexist
Class VI: Advanced sclerosing nephritis
Global sclerosis in more than 90% of the glomeruli

segmental (≥50% of the involved glomeruli have segmental lesions). The ISN / RPS work group proposes that all renal biopsies are evaluated by light microscopy (hematoxylin & eosin, silver - methenamine, PAS and trichrome), of immunofluorescence (IgG, IgA, IgM, C3, C1q, kappa and Lambda) and electrons.

All LN classifications emphasize in glomerular and vascular findings, which should always be complemented with activity indexes (AI) and chronicity (CI). This indexes will include significant tubulointerstitial findings (valuable for the prognosis), and give semiquantitative information of the pathological renal anatomy[30].

Although the ISN / RPS classification is used by the vast majority of the groups, there are several critical aspects to this: the prognostic studies were made based on the WHO classification; the presence of a single glomerulus with active or chronic lesions is enough to classify proliferative lesions as A or C[31]; the differentiation between global and segmental forms is not always easy and is of great importance in the pathophysiology and prognosis of LN; and does not include tubular lesions or arteriolar involvement.

Overall, histological classes I and II have an indolent course and III and IV, without treatment, present progressive renal damage[32]. However, histological transformation is frequent[27]; 66% of Class III LN patients and 18% Class V LN patients are spontaneously reclassified to class IV or to less severe classes with immunosuppressive therapy. The probability of doubling the creatinine, reach ESRD, or dye is higher in proliferative forms (32% class IV, 30% class III, 18% class V, 5% class II, $p < 0.025$) and in those with high activity indexes (AI 7 ± 6 vs. 5 ± 5, $p < 0.05$) and chronicity indexes (CI 4 ± 3 vs. 2 ± 2). Patients with extracapillary proliferation (crescentic GN) in the cell phase and interstitial fibrosis are considered to be at high risk for ESRD (70% at 90 months, $p < 0.0001$ vs. patients without these findings) [34]. No study evaluates the differences in the prognosis of patients with LN Class II with or without subepithelial or subendothelial deposits.

A very important aspect to evaluate the prognosis and define the treatment of patients with LN is the coexistence of nephropathy due to APS. The characteristic lesions are MAT (acute lesions) and fibrous intimal hyperplasia (chronic vascular lesions). It also includes atherosclerosis, organized thrombosis and ischemic subscapular focal cortical atrophy[35,36]. In a French cohort, 32% of the patients with LN had overlapping, histological findings suggestive of APS nephropathy, without systemic manifestations of APS in 22% of the cases. The noted histological findings were associated with systemic APS, lupus anticoagulant, hypertension, interstitial fibrosis and elevated creatinine. In a Colombian cohort of patients with APS[37], 16% of patients had some type of nephropathy (LN 11%, MAT 1% and diffuse proliferative glomerulonephritis with full house pattern and serology for persistently negative SLE 1%)[38].

Patients with SLE may present VT in the context of a thrombotic thrombocytopenic purpura[39] or have it only at the renal level, which may be present in up to 8.3% of the biopsies[40]. Patients with renal maturation present more severe clinical manifestations[41],

Figura 1

Glomerulonefritis proliferativa difusa IV-G (inmunofluorescencia)

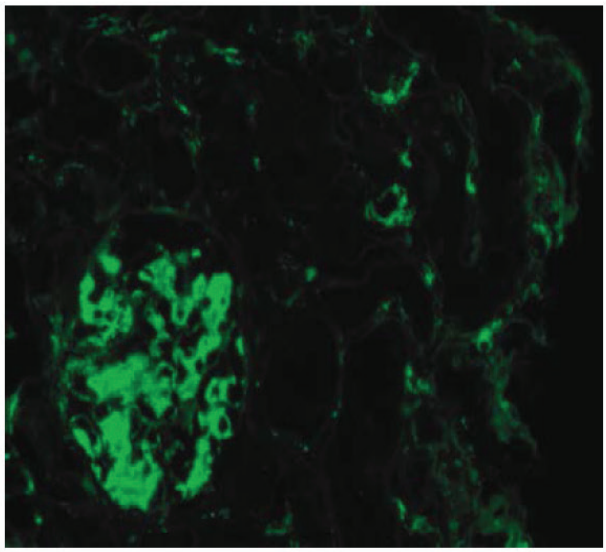


Figura 2

Nefritis lúpica proliferativa: depósitos inmunes subendoteliales (Microscopía electrónica)

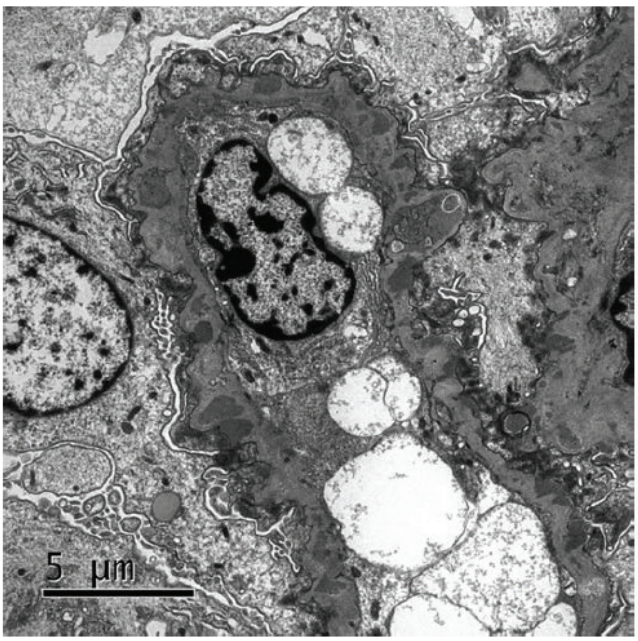
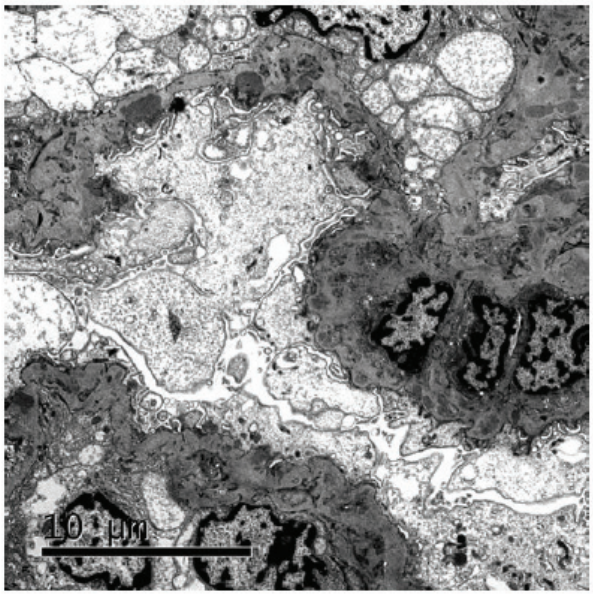


Figura 3
Nefritis lúpica V: Depósitos inmunes mesangiales, intramembranosos y subepiteliales y expansión del mesangio (Microscopía electrónica)



with more proteinuria, greater frequency of renal failure, hypertension and malignant hypertension, and worse prognosis in the short and long term with an increased risk of ESRD and death. Only 60.6% of them had microangiopathic hemolytic anemia41 so presence of thrombi in the glomeruli should be sought in all cases.

Special subgroups

Three additional aspects of histopathology should be analyzed when reviewing the renal biopsy of patients with SLE: Pauciinmune glomerulonephritis, focal and segmental, crescentic glomerulonephritis and vascular lesions.

In the focal and segmental LN, only a portion of the glomeruli and glomerular plume are affected, while the others are not affected; Immune deposits are often absent from focal lesions resembling the pauciimmunes found in ANCA-associated vasculitis[41-43]. Some authors find that patients classified by WHO as class III but with severe segmental affection (≥50% of the glomeruli) have a worse prognosis than patients with LN class IV[44-45]. By definition of the ISN / RPS classification, these patients could be classified as IV-G being in fact extensive segmental forms, with different pathophysiology and prognosis. Schwartz et al., 43 evaluated 83 renal biopsies with severe forms of LN that had proliferation or necrosis in ≥50% of the non-sclerotic glomeruli and classified by WHO as: severe segmental (class III with affection ≥50% of the glomeruli), global diffuse (class IV) and membranous (V ± III and V ± IV). These biopsies were recategorized to the ISN / RPS terminology and they found that 26.5% of the cases had segmental affection that compromised > 50% of the glomerular plume in ≥50% of the glomeruli. Although they had affection of more than 50% of the glomerular plume, in fact these patients had extensive, non-global segmental forms. The importance of this is that this subgroup of patients had a lower rate of remission, renal survival, stability of renal function and higher rates of ESRD and mortality than IV-G and IV-S glomerulonephritis. There are histological differences that could explain these findings; The biopsies performed with severe segmental glomerulonephritis have fewer subendothelial immune

deposits, hyaline thrombi and wire loops than global proliferative glomerulonephritis. This menaning they are more pauciimmune, however, they have more damage to the capillary wall[44].

Patients with rapidly progressive glomerulonephritis (RPGN) represent a separate subgroup; They typically have accelerated renal failure with loss of renal function in ≤3 months, evidence of glomerular injury with active urinary sediment and extracapillar proliferation[46]. Characterization of these biopsies by immunohistology shows 3 patterns: Type 1: granular pattern, characteristic of immune complex glomerulopathies, Type 2: linear pattern, basal glomerular antimembrane and Type 3: pauciinmune, observed in vasculitis associated with ANCA and glomerulonephritis Crescéntica pauciinmune.

Being SLE a disease with high humoral immunity, RPGN patients would be expected to have Type 1. However, severe forms of RPGN are described with prominent fibrinoid necrosis and extracapillary proliferation with minimal or absent subendothelial immune deposits and positive ANCA[47,48]. Crescentic glomerulonephritis is not uncommon in lupus. It is observed in 10% of all renal biopsies and in 21.7% of LN IV-G[49]; ANCA may play a pathogenic role in crescentic nephritis and segmental necrosis[45-50]. Patients with crescentic forms are less likely to have partial or complete remission and an increased risk of relapse, double creatinine values, have ANCA positive, and RD (IRCT en español). They present with more inflammation and interstitial fibrosis, tubular atrophy and indexes of activity and chronicity[47].

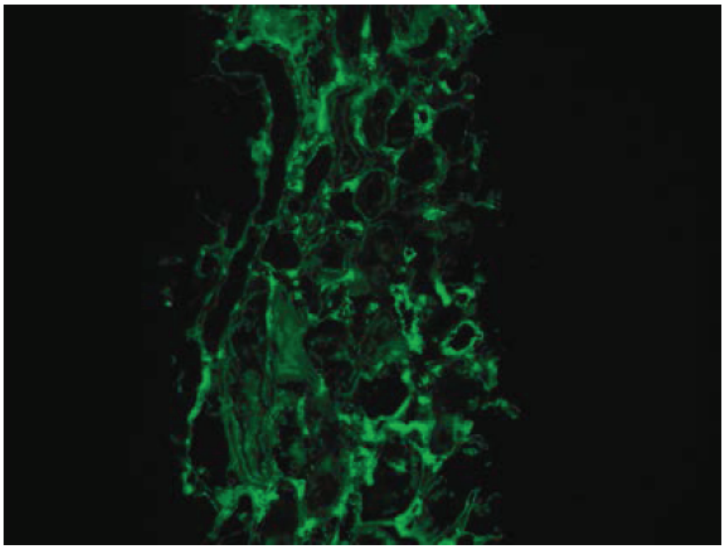
Another important aspect for the prognosis of LN is non-glomerular vascular compromise. Appel and et al., [51] described, for the first time, the term lupus vasculopathy as a non-inflammatory renal necrotizing microangiopathy, without thrombi and no association with APS. In a study of 169 renal biopsies of French patients with LN[52], arteriolesclerosis (49.7%), vascular wall (30.2%), lupus vasculopathy (24.3%), vasculitis (2.4%) and MAT (0.6%) were found. Patients with vascular involvement had a higher percentage of LN IV WHO, more hypertension, anemia, renal failure, proteinuria, nephrotic syndrome, hypocomplementemia, and thrombocytopenia than those without vascular affection. In Chinese patients, [43,53] the distribution of forms of vascular disease was different: 66% had vascular immune deposits, 12.6% arteriolesclerosis, 12% MAT, 6.3% non-inflammatory necrotizing vasculopathy, 1.4% vasculitis and 28% more than 2 forms of vascular injury. Patients with lupus vasculopathy presented more severe histological pictures, major AI and CI, endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, subendothelial deposits, tubular atrophy and interstitial fibrosis. They also presented more hematological cytopathies, hypocomplementemia and retention of sweat.

In patients with proteinuria of low magnitude, as in all other cases, the clinical - pathological correlation is inaccurate and may be severe LN in the initial phases. In the John Hopkins cohort[55] evaluated the findings of 21 kidney biopsies made while patients had proteinuria <1 gram / 24 hours or UPCR <1. In this group, which represented 6.4% of the sample, they found 5 cases of LN class III, one class IV, one class V and 6 class V associated to III or IV. One biopsy showed MAT. The only difference between patients with severe and mild histological forms was hypocomplementemia in the former. Therefore, patients with SLE with mild protenuria, clean sediment and normal renal function may have severe histological forms. C3 hypocomplementemia could suggest the presence of proliferative glomerulonephritis in this subgroup[56].

Clinical Manifestations and Predictors of Remission

LN is manifested in 6 different clinical-pathological patterns: dominant proteinuria with or without telescoped sediment, acute or chronic renal failure, nephritic syndrome with or without renal failure, RPGN, nephrotic syndrome and aggregated MAT[16]. In our setting LN is presented early in the natural history of the disease. In a cohort of 56 Colombian children, 16.1% had nephrotic syndrome and 14.3% nephrotic syndrome at diagnosis of SLE. In a population of 104 Colombian adults with SLE10, 35.7% had nephritis on diagnosis. In a cohort of 84 patients from the city of Medellín[17], we observed that LN was present on an average of 13.6 (0 - 168) months

Figura 4
Vasculopatía lúpica: depósito masivo de complejos inmunes y C4 en los capilares peritubulares



after diagnosis of SLE. The diagnosis of SLE and LN agreed in 36.9% of the patients. 63% of those who had LN presented it within the first 6 months and 72% during the first year.

The frequency of nephrotic syndrome varies among different ethnic groups. In the Colombian series analyzed, 25% of children13 and up to 38% of adults10,11,17 progress as stated. In the GLADEL8 cohort, 5.7% of whites, 6.7% of mestizos and 10.5% of Afro-Latin Americans with SLE had nephrotic syndrome. This manifestation is more frequent in African American lupus patients6 and less frequent in caucasians[57]. In our study, 40% of patients with LN III, 41% of LN IV, 50% of mixed forms and 70% of LN V, had proteinuria in the nephrotic range[11].

A very important aspect in the initial approach of patients with LN is to detect response predictors to the treatment, doubling of creatinine, ESRD and death. Baseline levels of creatinine and proteinuria, HT, anti-DNA antibodies, C3 and C4 hypocomplementemia, high AI and CI, and race are poor factors prognosis in patients with proliferative LN[16,32,58-65]. Failure to achieve partial (PR) or complete remission (RC) at 6 months is associated with poor prognosis in the long term and implies greater use of immunosuppressants[16]. In Asian patients the longer time to achieve remission and failure to achieve CR are relapse predictors and ESRD. On the other hand, normalization of creatinine in the first 48 weeks[67], proteinuria in the first 52[68] weeks and the decrease of this to less than 1 gram / 24 hours in the first 24[69] weeks, were good predictors of prognosis in Caucasian patients with LN.

In a cohort of Colombian patients with proliferative LN treated with steroids and cyclophosphamide (CP) or mycophenolate mofetil (MPM) 17 only 44% achieved PR or CR at 6 months (23.8% CR and 20.2% PR); 52.7% of the women and 80% of the men failed to achieve PR or CR at 6 months. The 23.4% of those who failed, reached at least PR at 12 months. In the multivariate analysis, the baseline alteration of renal function (OR 10.92, 95% CI 2.65 - 45.02, p = 0.001) and proteinuria in the nephrotic range (OR 9.81, 95% CI 1.85-54-04, p = 0.007) were Independent predictors of failure to achieve PR or CR at 6 months.

Treatment

The purpose of treatment of LN are: complete remision CR, or at least partial remision PR, at 6 months and not after 12 months; avoid irreversible renal damage, dialysis, transplantation and death, always looking for the lowest possible toxicity by medications; and preserving the quality of life[3].

The studies that evaluate the CR and PR outcomes are very heterogeneous by different definitions of response. The ACR defines CR as a glomerular filtration rate (GFR)> 90 mL / min / 1.73 m2 body surface area, proteinuria <500 mg / 24 hours (or UPCR <50 mg / mmol) and clean urinary sediment (<5 erythrocytes or leukocytes AP) [70]. The EULAR / ERA-EDTA guidelines propose similar CR and PR criteria but define renal function response as normal or "almost normal" (maximum GFR 10% below normal) [3].

The current immunosuppression regimens consist of an induction phase and a maintenance phase[2,3]. Induction therapy is done with steroids in combination with immunosuppressants, MMP or CPM. The suggested steroid regimen is intravenous methylprednisolone 500 mg / day administered in 3 doses (1 gram if extracapillary proliferation is demonstrated) followed by prednisolone 0.5-1 mg / kg / day in decreasing doses. If MMP is chosen the recommended dose is 2 - 3 grams / day. If CPM is chosen, there are 2 forms of administration: 0.75 - 1 gram / m2 / month for 6 months (National Institutes of Health, NIH) 71 or 750 mg, fixed dose, every 15 days for 6 doses EUROLUPUS scheme ") [57]. The EULAR / ERA-EDTA[3] guidelines only recommend the second scheme.

The classic studies of NIH[72,73] left us several lessons: in the treatment of LN steroids alone are inferior to their combination with cytotoxic; azathioprine (AZA) is inferior to CPM in induction of remission; short schemes (6 months) with CPM are long-term inferior to long-term (24-month) schedules; CPM in monthly or quarterly pulses confers less toxicity than daily oral administration and methylprednisolone pulses aid in subsequent use of lower doses of steroids. The use of CPM for periods of 2 years was associated with an increased risk of premature ovarian failure, leukopenia, infections and dysplasia of the cervix[72]. As an alternative with less toxicity, the EUROLUPUS study showed similar results although the benchmark was not the NIH scheme and included only Caucasian patients[57,69,74].

The controlled clinical studies (RCTs) that buy MMP and CPM in induction of proliferative LN remission[71, 74-78] have been tested in 2 recent meta-analyzes79,80 that showed no difference in the achievement of PR, CR and stabilization of renal function. CPM causes more alopecia and ovarian failure and MMP more diarrhea, but there were no differences in the presence of herpes zoster and major infections and the risk of ESRD. Death was the same for both drugs.

In the choice between CPM and MMP factors such as age[21], race[75], reproductive future and severity of the clinical presentation. While most clinicians prefer CPM for severe cases, successful stories of proliferative LN treatment with impaired renal function, vasculopathy, and crescentic glomerulonephritis has recently been reported with MMP[81-83]. Mycophenolate sodium[80] and tacrolimus84 have also been tested for induction of remission on proliferative LN with favorable results.

According to the recommendations of EULAR and ACR, patients who have not achieved PR or CR at 6 months should be reintroduced with methylprednisolone followed by a full dose of prednisolone combined with CPM or MMP (which was not chosen in the initial treatment). When there is failure to reinduction, treatment with RTX or cyclosporin A (CsA) is suggested.

Patients who reach PR or CR go to maintenance phase with MMF (1 - 2 g / day) or AZA (2 mg / kg / day). The therapy used to keep up the treatment should be continued for at least 3 years to avoid relapse[2,3,85]. Studies comparing MMP and AZA in maintenance therapy[86,89], grouped in a recent meta-analysis[90], showed no difference in relapse rates, IRCT, and death. Patients treated with AZA had more leukopenia and amenorrhea but there was no difference in adverse gastrointestinal events nor infections. The extension of the study ASPREVA[87] favors MMP and the study MAINTAIN[88] to AZA.

Rituximab, in the induction of proliferative LN remission has only been evaluated in a randomized controlled trial (RCT) [91] that did not demonstrate that it was better than the use of placebo in reaching a partial or complete response in patients receiving steroids and MMF. Patients in the RTX group had a greater decrease ≥ 50% in proteinuria (p = 0.04), required fewer CPM rescues (p = 0.006) and reached greater steroid savings, anti-DNA antibody titers, and normalization of C3 levels.

"Real-life" studies[92-100], mostly cohorts, show different results than the LUNAR study. Most of the patients received RTX due to failure to manage immunosuppressors, some in combination with MMP or CPM and others as monotherapy. The main conclusion of these studies is that RTX would be accurate in refractory cases of proliferative LN. This is the indication of the recommendations given by ACR and EULAR / ERA-EDTA. In patients from Colombia19, 75% of them with refractory LN to two or more immunosuppressants, a significant improvement of proteinuria, creatinine clearance, lupus activity measured by SELENA-SLEDAI and a decrease in steroid requirements were observed. After 12 months of treatment with RTX, 61.5% of the patients achieved PR or CR by the parameter proteinuria, and 33% by the parameter creatinine clearance. 20% of the patients required RTX retreatment, on average at 44 months (95% CI 10.1 - 50.1).

For patients with refractory LN (NB?)and associated VTE, plasma spares have been used and in cases of active LN and aggregated infection, intravenous gammaglobulin. None of these treatments has been tested in RCT, only in open studies[80].

The membranous glomerulonephritis with class III or IV associated, are treated as proliferative LN. The pure V forms represent between 0% and 19% of the cases published in Colombia[10-13]. The ACR2 and EULAR / ERA-EDTA[3] guidelines recommend initiating with prednisolone 0.5 mg / kg / day and MMF or AZA. If there is no favorable response at 6 months they suggest the use of CFM and methylprednisolone pulses. For refractory cases there is evidence of a favorable effect with CsA[101] and RTX[93,94].

Coadjuvant therapies are vital in the prognosis of LN. All patients with proteinuria ≥ 500 mg / 24 hours should receive inhibitors of the angiotensin converting enzyme or angiotensin receptor blockers. These drugs reduce up to 30% proteinuria values and delay the duplication of creatinine and CRIT in non-diabetic patients[2,3]. Blood pressure targets ≤130 / 80 and strict control of dyslipidemia are indicated. Hydroxychloroquine decreases the damage accumulated including in renal function and relapses. It should be received by all patients with SLE and LN, excluding those with contraindications[102,103].

Collaborations

Adriana Flórez Vargas, Nephropathologist, Fundación Santa Fe de Bogotá and Mauricio Lopera, Nephrologist RTS - Baxter Medellín, by histopathological images.

Ackwonledgements

To the doctors Carolina Muñoz Grajales, Javier Darío Márquez Hernández and Carlos Jaime Velásquez Franco, rheumatologists of the Hospital Pablo Tobón Uribe for their valuable participation in the investigations in lupic nephritis in the city of Medellín.

Conflicts of interest and sources of funding:

The author did not receive funding to carry out this review and has no conflicts of interest to report.

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