Reumatología Clínica

Editorial

Lupus Nephritis: Advances in the Knowledge of its Immunopathogenesis Without the Expected Therapeutic Success?☆

Nefritis lúpica: ¿avances en el conocimiento de su inmunopatogénesis sin los esperables logros terapéuticos?

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Systemic lupus erythematosus (SLE) is a polygenic and multifactorial syndrome, characterized by deep and diverse alterations in immunoregulation and loss of tolerance, and pathogenic autoantibody production is expressed by multiorgan involvement; nephritis (NL) is common and causes high morbidity and mortality.[1]

In SLE there is an increase in apoptosis gene dysregulation as a result of alterations in the handling and purification of nucleosomes and chromatin, formation of autoantibodies and immune cell dysfunction (antigen presenting macrophages, T and B cells). This translates into a tissue infiltration of immune cells, increased cytokine expression (interferon, interleukin 17, 6 and tumor necrosis factor, among others), and as the production of anti-DNA autoantibodies that are associated with endothelial dysfunction as well as of other cells and tissues, and their consequent failure.[1]

LN is accompanied by structural and functional modification of podocytes and proteins involved in tissue damage. Nucleosomal DNA and immune complexes activate TLR9 receptors on B cells, and on plasmacytoid dendritic cells. B lymphocyte stimulator (BLyS or BAFF-activating factor), proliferation-inducing ligand (APRIL) and weak inducers of apoptosis from the TNF family (TWEAK) are cytokines involved in inflammatory processes and autoimmunity. Viral and bacterial products and drugs (some that decrease DNA methylation) intrarenally stimulate immune cells, leading to proteinuria. Ultraviolet light induces apoptosis of keratinocytes, increasing the load of dead cells and their inefficient clearance and exacerbates SLE. Immune complexes are related to the type, duration and severity of LN, with mesangial, subendothelial or subepithelial deposits, and the concurrent activation of complement. The immune complexes bind to receptors (Fc and complement TLR), activate kidney cells (macrophages, dendritic cells, podocytes), attract leukocytes (via adhesion molecules and complement

proteins) increase the expression and cytokine production (IL-17 induces nephrocytopathic CD3+/CD4+ or CD3+CD4−/8− T cells), activate endothelium, condition extracapillary proliferation (crescent formation), and periglomerular inflammation and sclerosis.[1]

One of the challenges in treating SLE is represented by LN. Steroids are the initially considered cornerstone of treatment but by themselves are not effective enough to achieve complete remission and preserve function.[1–3] Although combination therapy with cyclophosphamide (CFM) will achieve better results, sustained remission is <40%, with loss of renal function in >40% of those with type iv LN, which emphasizes the need for other therapeutic modalities; in addition, relapses are frequent, 27%–66%, particularly when inappropriate therapy is employed and partial responses obtained, but may be lower with mycophenolate mofetil (MMF).[4–7] Relapses may be proteinuric nephritic or associated to different biomarkers that exceed the classical increments in double-stranded DNA (dsDNA) and hypocomplementemia; they include monocyte chemoattractant protein (MCP-1), chemokines, gelatinase associated lipocalin neutrophil (NGAL), and urinary TWEAK among others.[8,9] Accepted as risk factors associated with relapse are age <30 years, male gender, African American ethnicity, the delay in the initiation of treatment, prolonged time to achieve remission, persistent hypocomplementemia in spite of response, the absence of a complete response, a high SLE activity score, hypertension, neurological manifestations and low doses of immunosuppressants, besides the presence of microangiopathy and extracapillary proliferation.[6,7,10–12]

The EULAR, in conjunction with the European Renal and Dialysis and Transplant Association, suggests performing a biopsy when faced with any signs of kidney disease in order to classify histology, with the goal of achieving a complete response (proteinuria creatinuria relationship <50 mg/mmol or proteinuria <0.5 g/d; normal or near normal glomerular filtration rate [GFR]: <10% below normal in previous abnormality) or partial response (>50% reduction in proteinuria and normal or near-normal GFR). In LN class III and IV, induction therapy is done with MMF/mycophenolic acid (MMF/MPA) or low-dose steroids in combination with CFM and maintained with MMF/MPA or azathioprine, for refractory LN

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class V, calcineurin inhibitors (ICN) and rituximab (B cell depleting therapy) and adjunctive therapy with antimalarials, inhibitors of angiotensin converting enzyme or AT2 blockers (for hypertension and proteinuria), statins (dyslipidemia, endothelial dysfunction, immune modulator), aspirin, and anticoagulant (for APS and morbid proteinuria) and vitamin D (immunomodulator) are employed, all with periodic monitoring of creatinine, urinalysis, anti-dsDNA and complement. Children should receive the same therapy. Pregnancy should be planned when there is SLE inactivity, and low doses of steroids, antimalarials, azathioprine and CNI may be employed; in special cases statins could be considered.[6,7,12–16] We advise the performance of a renal biopsy in the first weeks, something which is desirable for all patients with SLE, particularly those with biomarkers (dsDNA, hypocomplementemia) and in children who have very high prevalence of LN (80%). The need for a second biopsy is evident when an increase in proteinuria, sediment alterations or relapse is present and in patients showing deterioration of GFR or to reach a differential diagnosis when faced with an increase in biomarker activity, thrombotic microangiopathy, podocytopathy, when treatment is ineffective and to establish prognosis (presence of crescents or extracapillary proliferation and tubulointerstitial fibrosis).[15–18] MMF is at least as effective and safe as CFM for both induction and maintenance, even in poor prognosis LN.[1,14,19] The therapeutic response is not homogeneous, with mixed results in hispanics[4,20,21]; we should consider adjuvant therapy (antimalarials and statins) to enhance the response and prevent relapse; azathioprine has a lower response in maintainance.[22–24]

Methotrexate may be useful in LN, but should be limited to patients with normal renal function.[25–27]

Tacrolimus (TL), a specific CNI, due to its antiproteinuric effect is effective even at low doses, with higher responses and greater safety profile than CFM, as evidenced by a meta-analysis of five controlled studies with 225 patients, with higher rates of complete response (RR 1.61, 95% CI 1.17–2.23, P<.004), response, and albumin levels and rates of negative dsDNA result, lower disease activity scores (SLEDAI), proteinuria and menstrual and gastrointestinal adverse events. Although limited to one ethnic group, with little follow-up (6 months) and only one multicenter study, it seems an excellent choice, with rapid and sustained efficiency, high response rates, significant reduction of proteinuria, increase and preservation of GFR.[28] Recently a one-year open study with 40 patients demonstrated the advantage of TL over CFM, with a greater decrease in proteinuria starting at the second week (5±1.91 g/d; 2.54±1.68 g/d, P<.001), greater partial remission within the first month 65% (13/20) with TL vs none with CFM (P<.001), and the incidence of complete remission at 12 months 5 and 55 and 75% vs TL. 15 CFM and 40% (P=.008 and P=.025 respectively).[24,29]

B lymphocyte depleting therapy with rituximab in refractory LN led to an excellent response in uncontrolled studies, even without using CFM or steroids; its action is not limited to B depletion, but to increased regulatory T cells and offers some advantages over CFM.[26,30–32] The LUNAR, trial with 144 patients from 52 centers achieved partial or complete response in 45.8% vs 56.9% with MMF, although with a reduced CFM requirement and greater decrease in DNA and increased complement levels (P=.007 and P=.03 respectively).[33,34] Although large, controlled studies are needed, there is evidence that rituximab favorably altered histological[35] classes.

Abatacept (a drug that blocks T cell costimulation), monoclonal antibodies against interferon (rontalizumab, sifalimumab), other B cell depleting therapies (epratuzumab: anti-CD22), or antistimulant or antireceptor treatment (atacicept vsTACI, anti-BAFF) may have some utility in LN.[36] Belimumab, an IgG1 monoclonal anti-BLyS, is associated with reduced activity and lower relapse in SLE as well as increased complement levels and a decrease in anti-dsDNA titers. Although recently approved, no experience with severe LN exists, and is currently not very effective in LN with a better response seen with MMF.[37] There is a study currently underway with anti-TWEAK ("ATLAS"), a double-blind controlled trial for patients with Class III and IV LN with high expectations.[38] Other biological drugs directed against cytokines (IL-6, IL17 and IL-10 among others) as well as those against some complement proteins, may have a role in selected groups of patients with LN, but lack controlled studies.[39–42]

Intravenous immunoglobulin may be as effective as CFM, and it seems that plasmapheresis accelerates the therapeutic response, particularly in LN with extracapilar[43] proliferation. Among the therapeutic options, biological drugs and stem cell transplantation of mesenchymal cells could be employed in refractory LN. Note that steroids may not be essential for the induction of remission and may be deleterious.[24,26,30,44]

It seems that silent nephritis has a greater frequency than has been previously considered, associated to proliferative classes in half of patients, even without clinical expression or alterations in urinalysis; reiterating the fact that a biopsy should be performed in high-risk groups (pediatric patients, men) and/or those with the aforementioned[45] biomarkers.

Preeclampsia occurs in 9%–35% of patients with SLE and pregnancy, and fetal loss and intrauterine growth retardation occurs twice as frequently or more, particularly in LN, which is associated with poor maternal and fetal outcome, especially regarding kidney function, increased proteinuria, GFR <60, antiphospholipid and antiphospholipid antibody syndrome; severe renal impairment and dialysis requirement is rare with proper treatment, a pregnant woman can receive immunomodulators (even rituximab) except MMF, leflunomide, methotrexate and CFM, particularly in the first trimester.[46]

As stated previously, LN remains a diagnostic and treatment challenge despite advances in physiopathology. MMF, CFM, TC and rituximab are effective for induction of remission, among other drugs, and the physician must add other immunomodulatory adjuvants such as statins, vitamin D, antimalarial and anticoagulants, and although the definitive role of steroids is not clearly defined, the therapeutic mixture of immunomodulators and adjuvants achieves higher rates of complete and sustained remission, but the need for long-term controlled studies to define both the scope of the various combinations and subgroups of potential response of the various therapeutic modalities is evident.

References

1. Kulkami OP, Anders HJ. Lupus nephritis. How latest insights into its pathogenesis promote novel therapies. Curr Opin Rheumatol. 2012;24:457–65.
2. Arends S, Grootscholten C, Derksen RH, Berger SP, de Sévaux RG, et al., Dutch working party on systemic lupus erythematosus. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. Ann Rheum Dis. 2012;71:966–73. http://dx.doi.org/10.1136/annrheumdis-2011-200384 [Epub 2011 November 29].
3. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46:2121e31.
4. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al., and the Aspreva Lupus Management Study Group. Mycophenolate mofetil *versus* cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20:1103–12.
5. Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. J Rheumatol. 2011;38:69–78.
6. Sprangers B, Monahan M, Appel GB. Diagnosis and treatment of lupus nephritis flares—an update. Nat Rev Nephrol. 2012:709–17.
7. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al., American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64:797–808.

8. Xuejing Z, Jiazhen T, Jun L, Xiangqing X, Shuguang Y, Fuyou L. Urinary TWEAK level as a marker of lupus nephritis activity in 46 cases. J Biomed Biotechnol. 2012. http://dx.doi.org/10.1155/2012/359647.

9. Brunner HI, Bennett MR, Mina R, Suzuki M, Petri M, Kiani AN, et al. Association of noninvasively measured renal protein biomarkers with histologic features of lupus nephritis. Arthritis Rheum. 2012;64:2687–97.

10. Hu WX, Liu ZZ, Chen HP, et al. Clinical characteristics and prognosis of diffuse proliferative lupus nephritis with thrombotic microangiopathy. Lupus. 2010:1–8.

11. Yu F, Tan Y, Liu G, Wang SX, Zou WZ, Zhao MH. Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis. Kidney Int. 2009;76:307–17.

12. Bertsias, G.K. et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. Available from: http://dx.doi.org/10.1136/annrheumdis-2012-201940

13. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis. 2010;69:61–4.

14. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69:2083–9.

15. Baranowska-Daca E, Choi YJ, Barrios R, Nassar G, Suki WN, Truong LD. Nonlupus nephritides in patients with systemic lupus erythematosus: a comprehensive clinicopathologic study and review of the literature. Hum Pathol. 2001;32:1125–35.

16. Cheunsuchon B, Rungkaew P, Chawanasuntorapoj R, Pattaragarn A, Parichatikanond P. Prevalence and clinicopathologic findings of antiphospholipid syndrome nephropathy in Thai systemic lupus erythematosus patients who underwent renal biopsies. Nephrology. 2007;12:474–80.

17. Gunnarsson I, Sundelin B, Heimbürger M, Forslid J, van Vollenhoven R, Lundberg I, et al. Repeated renal biopsy in proliferative lupus nephritis—predictive role of serum C1q and albuminuria. J Rheumatol. 2002;29:693–9.

18. Miranda JM, Garcia-Torres R, Jara LJ, Medina H, Cervera H, Fraga A. Renal biopsy in systemic lupus erythematosus: significance of glomerular thrombosis. Analysis of 108 cases. Lupus. 1994;3:25–9.

19. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al., for the ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886–95.

20. Rivera TL, Belmont HM, Malani S, Latorre M, Benton L, Weisstuch J, et al. Current therapies for lupus nephritis in an ethnically heterogeneous cohort. J Rheumatol. 2009;36:298–305.

21. Kallenberg CGM. Could we abandon cyclophosphamide in systemic vasculitis and lupus nephritis? Ann Rheum Dis. 2012:1–4. http://dx.doi.org/10.1136/annrheumdis-2012-202195.

22. Costedoat-Chalumeau N, Galicier L, Aumaitre O, Francés E, LeGuern V, Lioté F, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2012;0:1–7. http://dx.doi.org/10.1136/annrheumdis-2012-202322.

23. Abud-Mendoza C, de la Fuente H, Cuevas-Orta E, Baranda L, Cruz-Rizo J, González-Amaro R. Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. Lupus. 2003;12:607–11.

24. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, et al. Treatment for lupus nephritis. Cochrane Database Syst Rev. 2012;12. http://dx.doi.org/10.1002/14651858. CD002922.pub3.

25. Abud-Mendoza C, Sturbaum AK, Vazquez-Compean R, Gonzalez-Amaro R. Methotrexate therapy in childhood systemic lupus erythematosus. J Rheumatol. 1993;20:731–3.

26. Vigna-Pérez M, Hernández-Castro B, Paredes-Saharopulos O, Portales-Pérez D, Baranda L, Abud-Mendoza C, et al. Clinical and immunological effects of rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther. 2006;8:R83. http://dx.doi.org/10.1186/ar1954. Published online 2006 May 5, PMCID: PMC1526618.

27. Lehman TJ, Edelheit BS, Onel KB. Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis. Ann Rheum Dis. 2004;63:321–3.

28. Deng J, Huo D, Wu Q, Yang Z, Liao Y. A meta-analysis of randomized controlled trials comparing tacrolimus with intravenous cyclophosphamide in the induction treatment for lupus nephritis. Tohoku J Exp Med. 2012;227:281–8.

29. Wang S, Li X, Qu L, Wang R, Chen Y, Li Q, et al. Tacrolimus versus cyclophosphamide as treatment for diffuse proliferative or membranous lupus nephritis: a non-randomized prospective cohort study. Lupus. 2012;21:1025–35.

30. Abud-Mendoza C, Moreno-Valdés R, Cuevas-Orta E, Borjas A, Aranda F, Irazoque F, et al. Treating severe systemic lupus erythematosus with rituximab. An open study. Reumatol Clin. 2009;5:147–52.

31. Díaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martínez-Berriotxoa A, et al., UK-BIOGEAS Registry. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012;5:357–64.

32. Andrade-Ortega L, Irazoque-Palazuelos F, López-Villanueva R, Barragán-Navarro Y, Bourget-Pietrasanta F, Díaz-Ceballos MA, et al. Eficacia de rituximab comparado con ciclofosfamida en pacientes con manifestaciones graves de lupus eritematoso generalizado. Estudio aleatorizado y multicéntrico. Reumatol Clin. 2010;6:250–5.

33. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab (LUNAR) study. Arthritis Rheum. 2012;64:1215–26.

34. Weidenbusch M, Römmele C, Schröttle A, et al. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. Nephrol Dial Transplant. 2012, in press.

35. Gunnarsson I, Sundelin B, Jónsdóttir T, Jacobson SH, Henriksson EW, van Vollenhoven RF. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum. 2007;56:1263–72.

36. Postal M, Costallat LTL, Appenzeller S. Biological therapy in systemic lupus erythematosus. Int J Rheumatol. 2012:578641. http://dx.doi.org/10.1155/2012/578641.

37. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, et al., for the BLISS-52 and -76 Study Groups. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus. 2013;22:63–72.

38. Michaelson JS, Wisniacki N, Burkly LC, Putterman C. Role of TWEAK in lupus nephritis: a bench-to-bedside review. J Autoimmunity. 2012;39:130–42.

39. Shirota Y, Yarboro C, Fischer R, Pham TH, Lipsky P, Illei GG. Impact of anti-interleukin-6 receptor blockade on circulating T and B cell subsets in patients with systemic lupus erythematosus. Ann Rheum Dis. 2013;72:118–28.

40. Sifuentes-Giraldo WA, García Villanueva MJ, Boteanu AL, Iglesias AL, Zea-Mendoza AC. Nuevas dianas terapéuticas en el lupus sistémico (parte 2/2). Reumatol Clin. 2012;8:263–9.

41. Sifuentes-Giraldo WA, García Villanueva MJ, Boteanu AL, Iglesias AL, Zea-Mendoza AC. Nuevas dianas terapéuticas en el lupus sistémico (parte 1/2). Reumatol Clin. 2012;8:201–7.

42. Su DL, Lu ZM, Shen MN, Li X, Sun LY. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. J Biomed Biotechnol. 2012. http://dx.doi.org/10.1155/2012/347141. ID 347141.

43. Wenderfer SE, Thacker T. Intravenous immunoglobulin in the management of lupus nephritis. Autoimmune Dis. 2012:589359. http://dx.doi.org/10.1155/2012/589359.

44. Fischer-Betz R, Chehab G, Sander O, Vordenbäumen S, Voiculescu A, Brinks R, et al. Renal outcome in patients with lupus nephritis using a steroid-free regimen of monthly intravenous cyclophosphamide: a prospective observational study. J Rheumatol. 2012;39:2111–7.

45. Wakasugi D, Gono T, Kawaguchi Y, Hara M, Koseki Y, Katsumata Y, et al. Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. J Rheumatol. 2012;39:79–85.

46. Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. Lupus. 2012;21:1271–83.