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Lupus nephritis: in search of a better future

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The Spanish Society of Nephrology and the Spanish Society of Internal Medicine recently presented a consensus document for the diagnosis and treatment of lupus nephritis,[1] which was intended to facilitate diagnostic and therapeutic decision-making regarding patients with systemic lupus erythematosus (SLE) and altered renal function.

This document, composed of five chapters and based on an exhaustive literature review, summarises a list of recommendations that brings current knowledge on the subject up to date and provides support, with various levels of evidence, for important decisions in the clinical care of lupus nephritis patients.

The collaboration between these two scientific societies was based on solid multidisciplinary foundations that must be considered for these patients with chronic diseases, from the initial stages of diagnosing and evaluating the type of renal damage, choosing the proper treatment, and monitoring. The essential objectives are to identify problems as early as possible and that can be prevented or treated as effectively as possible in order to achieve the highest level of remission for as long as possible.

Several studies have been published in recent decades that have provided new and sometimes highly awaited and important pieces of evidence that have facilitated a personalised and effective treatment of patients with lupus nephritis, with fewer complications. This new panorama is driving important advancements in the quality and quantity of life of these patients by improving the control of the immunological activity of SLE and the recovery of deteriorated renal function.

Renal involvement occurs in half of all patients with SLE, and plays a very important role in this disease, since it independently affects patient survival. Therefore, evaluating proteinuria, urinary sediment, and glomerular filtration rate must all be prioritised in patients with SLE, both in the initial doctor's visit and in subsequent check-ups. Additionally, a renal biopsy performed following established recommendations guarantees a precise evaluation of the type and extent of the renal damage, justifying the choice of procedures that are not without risk. The decision of which treatment to choose among the possible alternatives listed in the guidelines must be supported by individual clinical and pathological characteristics, keeping in mind that the patient must not be under-treated (greater risk of irreversible organ damage) or over-treated (more complications and greater severity).

We have recently been able to understand some of the mechanisms involved in the development of lupus nephritis in the context of hyperactive B lymphocytes, caused by an altered Lyn protein that usually regulates the activation of these B-cells. Among the culprits are basophils and mast cells, two of the cell lineages related to the pathogenesis that involves Th2 lymphocytes.[2] These are major advancements in determining the origin of the disease and identifying therapeutic targets.

As one of the most notable milestones in the treatment of lupus nephritis, we must mention cyclophosphamide pulses along with steroids. The widespread use of this treatment allowed for reaching a higher rate of remission, both of lupus disease in general and renal damage in

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particular. Currently, any treatment that might act as an alternative to cyclophosphamide must first prove that it does not have inferior potency or efficacy and that it can provide additional advantages to cyclophosphamide, at least in three of the areas where we still need to make progress: adverse effects, recurrence, and unresponsive patients. Although we have reached high levels of remission using cyclophosphamide, the price of the treatment and the rates of recurrence are very high and oblige us to maintain patients on immunosuppressants for long periods of time, sometimes lifelong.

Fortunately, several well designed studies with control groups have produced therapeutic advancements in this field. Firstly, the discovery that induction doses of cyclophosphamide during shorter time periods were capable of achieving the same efficacy, even at lower doses,[3,4] which opened the door for more recent developments. This yielded mycophenolate (a "friendly" drug following successes in kidney transplants) as an alternative to cyclophosphamide, both in induction[5] and maintenance[6,7] phases, for the majority of patients with lupus nephritis. It offers some advantages over azathioprine in efficacy, interval between recurrences, and time to salvage therapy.

In the chapter on resistance to cyclophosphamide and mycophenolate, the guidelines describe where a repeated renal biopsy might be performed to search for changes and where administering immunosuppression along with triple therapy. It also underscores that some patients may respond well to lymphocyte-depleting biological agents, calcineurin inhibitors, or immunoglobulins, where evidence in support is still not so well established. In these situations, the recommendations are still a source of controversy, probably due to the heterogeneity of clinical presentations and several other factors that may influence the disparity in patient responses.

When the experience gained in treating patients with lupus nephritis is measured in decades instead of years, certain precautions take on much greater importance. In this sense, the guidelines clearly take into account the current policy of steroid saving, a strategy that must always influence our therapeutic recommendations since, once reaching the chronic stage of the disease, we must imagine the patient after 20 or more years of treatment. Along this same line, concomitant treatment with anti-proteinuria drugs has gained major importance, especially in patients with resistant or residual proteinuria, which we now know is never innocuous, and the lower, the better. If we only consider the kidney and its alterations, we lose perspective and objectivity regarding protection against cardiovascular risk and bone damage, hindering an overall therapeutic approach to patients with SLE. Whenever possible, we should take a multidisciplinary approach to treatment, since this type of collaboration provides major advantages in disease prevention (arteriosclerosis, prophylaxis against infections, and bone and joint complications) and under certain circumstances (renal failure, gestation, and anti-phospholipid syndrome), even in patients with apparently good levels of remission of nephritis and SLE.

The consensus document also includes a number of recommendations for special situations, including actions to take in advanced stages of chronic kidney disease and possibilities for renal replacement therapy, which will be needed in almost 20% of all patients with lupus nephritis,[8] a complication that currently does not prevent reaching good results with different dialysis treatments or kidney transplant.[9]

When we speak of the future, we always imagine new drugs that will be better at treating lupus nephritis, and without a doubt, this is the most promising avenue for development. This is the field where we have experienced the greatest progress in the past and so should it be in the future, although we must keep in mind already existing drugs, such as anti-malarial medications, which are now employed as concomitant treatments. The drugs that will constitute the future therapeutic arsenal against lupus nephritis will be much closer to the ideal, since they will focus on specific targets and produce fewer side effects. These treatments will be adjusted for each individual and level of renal involvement. With the aid of biological markers, we will be able to better determine the severity of the disease and response to treatment than using proteinuria levels, urinary sediment, and creatinine clearance. We will also be able to better distinguish between a flare of lupus activity and other non-immunological processes that involve organ damage. Although this currently seems like a complicated task, it is close to being a reality.

With these ambitious objectives, the SEMI-SEN guidelines for the diagnosis and treatment of lupus nephritis should provide a useful tool that facilitates decision- making, supported by the best evidence currently available, with idea that the present and future condition of patients with lupus nephritis can be undoubtedly better.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

REFERENCES

1. Ruiz Irastorza G, Espinosa G, Frutos MA, Jiménez Alonso J, Praga M, Pallarés L. Diagnóstico y tratamiento de la nefritis lúpica.

Documento de consenso del Grupo de Enfermedades Autoinmunes Sistémicas (GEAS) de la Sociedad Española de Medicina Interna (SEMI) y de la Sociedad Española de Nefrología (S.E.N.). Nefrologia 2012;32 Suppl(1):1-35.
2. Charles N, Hardwick D, Daugas E, Illei GG, Rivera J. Basophils and the T helper 2 environment can promote the development of lupus nephritis. Nat Med 2010;16:701-7.
3. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Damieli MG, et al. Immunosupressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial - A randomized trial of low dose versus high dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121-31.
4. Frutos MA. Ciclofosfamida intravenosa en nefritis lúpica: veinte años reduciendo dosis. Nefrologia 2007;27:12-22.
5. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103-12.
6. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathiprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886-95.
7. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppresion in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis 2010;69:2083-9.
8. Costenbader KH, Desai A, Alarcón GS, Hiraki LT, Shaykevich T, Brookhart MA, et al. Trends in the incidence, demographics and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995-2006. Arthritis Rheum 2011;63:1681-8.
9. Contreras G, Mattiazzi A, Schultz Dr. Kidney transplantation outcomes in African-, Hispanic- and Caucasian-Americans with lupus. Lupus 2012;21:3-12.

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