Reumatol Clin. 2016;12(4):210–215

Reumatología Clínica

www.reumatologiaclinica.org

Review Article

Rituximab in Lupus Nephritis: A Non-systematic Review☆

Luis Zurita Gavilanes,[a,b] Aldo Costa Valarezo[b,*]

[a] Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA), Guayaquil, Ecuador
[b] Facultad de Ciencias Médicas, Universidad Espíritu Santo, Guayaquil, Ecuador

ARTICLE INFO

Article history:
Received 14 July 2015
Accepted 15 January 2016
Available online 21 June 2016

Keywords:
Rituximab
Nephritis
Lupus

ABSTRACT

Lupus nephritis (LN) is a common and severe complication in patients with lupus. Current therapy is based on immunosuppressive drugs and glucocorticoids. Recently, rituximab has been proposed as an alternative treatment for LN. Rituximab is a monoclonal antibody directed against the CD20 antigen receptor on B cells. The aim of this review is to summarize all the available information about rituximab in LN. Eleven studies were found; three of them were observational studies (2 prospective and 1 retrospective) and eight were clinical trials (7 open-label studies and only 1 randomized controlled trial [RCT]). The evidence is insufficient to establish the role of rituximab in the treatment of LN. Results from the only RCT, which were negative, suggest a clinical benefit in black people. Further studies must confirm this hypothesis. Controlled clinical trials involving adaptive randomization are required to establish the real benefit of rituximab in LN.

Rituximab en nefritis lúpica: una revisión no sistemática

Palabras clave:
Rituximab
Nefritis
Lupus

RESUMEN

La nefritis lúpica (NL) es una complicación común y grave del lupus. En la actualidad, la terapia está basada en inmunosupresores y glucocorticoides. Recientemente se ha planteado como posible tratamiento al rituximab, un anticuerpo monoclonal dirigido contra el antígeno CD20 de los linfocitos B. El objetivo de la presente revisión es recopilar la información disponible hasta el momento acerca del uso de rituximab en NL. Se encontraron 11 estudios, 3 observacionales (2 prospectivos y uno retrospectivo) y 8 ensayos clínicos (7 abiertos y solo uno aleatorizado controlado). La evidencia es insuficiente para establecer el papel del rituximab en la terapia de la NL. Resultados del único ensayo clínico aleatorizado y controlado, el cual falló en demostrar una mejoría clínica significativa, indican un posible beneficio en pacientes de raza negra. Futuros estudios deben confirmar dicha hipótesis. Se proponen ensayos clínicos controlados, con aleatorización adaptativa, para establecer el verdadero beneficio con rituximab en NL.

Introduction

Lupus nephritis (LN) is a common but serious complication of systemic lupus erythematosus (SLE). The prevalence of SLE ranges between 1.4% and 21.9% and the incidence between 7.4 and 159.4 cases per 100 000 population.[1] It is known that 60% of the SLE patients will develop LN[2] and more than 25% of these patients will develop end-stage renal disease 10 years after the onset of renal symptoms.[1]

The main clinical features are proteinuria and microscopic hematuria. Less common findings are macroscopic hematuria and hypertension.[2] Certain histopathological changes can result in different clinical presentations. Thus, although in LN, the histopathological findings obtained from renal biopsy are not necessary for the diagnosis, they are of the utmost importance for the classification of the disease.

☆ Please cite this article as: Zurita Gavilanes L, Costa Valarezo A. Rituximab en nefritis lúpica: una revisión no sistemática. Reumatol Clin. 2016;12:210–215.

* Corresponding author.
E-mail address: aldocosva_01@hotmail.com (A. Costa Valarezo).

Different pathophysiological mechanisms have been involved in the development of LN in SLE patients. A combination of genetic, environmental and immunological factors mediate the processes that result in the renal damage.[1–4] Of special importance for the present review is the role of the B cells, which are hyperactive in SLE. The B cells mediate and regulate antibody production, interact with memory T cells and stimulate proinflammatory cytokine production, all of which makes them essential components of the pathophysiology of LN.[1] It is for these reasons that the use of rituximab is proposed. Rituximab is a chimeric monoclonal antibody (murine/human) approved by the United States Food and Drug Administration in 1997.[5] This monoclonal antibody is directed against CD20, an antigen expressed on the surface of mature and immature B cells. CD20 regulates the initiation of the cell cycle. The binding of the antibody to Fc receptor induces apoptosis and cytotoxicity, mediated by both complement and antibodies.

Treatment of LN was based for some years on glucocorticoids. This therapy had the disadvantage of the high morbidity and mortality rates resulting from the high doses administered, as well as its inability to arrest the progression of the renal disease.[6] One proposal for solving this problem was the use of immunosuppressive agents, which were evaluated in a landmark clinical trial performed to determine the long-term survival of 107 LN patients. This trial revealed a difference in terms of renal function preservation, but said difference was statistically significant only for the combination of intravenous (IV) cyclophosphamide and low-dose, rather than high-dose, prednisone. No differences in the mortality rate were observed.[7]

At the present time, therapy for LN consists of an induction phase followed by a maintenance phase. The majority of the patients with active proliferative LN are initially treated with pulsed methylprednisolone for 3 days, followed by a period of oral prednisone at an initial dose that is tapered until it reaches the minimum effective dose. The guidelines for the management of LN of the American College of Rheumatology recommend oral mycophenolate mofetil (2–3 g/day) or intravenous cyclophosphamide, together with glucocorticoid therapy as induction therapy for classes III and IV LN (level A evidence).[8] In general, high doses of intravenous cyclophosphamide (500–1000 mg/m^2 each month for 6 months), although the results observed with lower doses of intravenous cyclophosphamide (500 mg/m^2 every 2 weeks for 6 months) were similar to those of the high-dose regimen.[9] The recommendation for maintenance therapy is the use of mycophenolate mofetil or azathioprine. The choice of one or the other should be made on an individual basis.

Resistance to standard induction therapy and recurrences during treatment have led to the consideration of new therapeutic strategies that include the use of rituximab as a third line of treatment, especially in focal or diffuse proliferative LN, the clinical courses of which are more aggressive than those of other classes of LN. It is difficult to determine the incidence of resistance to the initial treatment in LN patients simply because it is difficult to determine remission in these individuals, as this concept varies depending on the criteria applied. In general, remission has been confirmed by the presence of inactive urinary sediment, reduced proteinuria and normalization of the serum creatinine level. On the other hand, treatment resistance is defined as the failure to respond after 6 months of glucocorticoid and immunosuppressive therapy.[8] The first step in patients who fail to respond to the initial treatment will depend on the immunosuppressive agent being used and will consist in switching to another immunosuppressive medication. Thus, if cyclophosphamide was being administered, it should be replaced by mycophenolate mofetil and vice versa. If this strategy were to fail to achieve remission, the use of rituximab is proposed (level C evidence).[8]

The LUNAR study (A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis)[10] is the first randomized, parallel-group, placebo-controlled clinical trial to incorporate rituximab into therapy for LN, in combination with glucocorticoids and mycophenolate mofetil. Its publication in 2012 raised great expectation, as its results would confirm those observed in previous studies.

The purpose of the present literature review is to retrieve the most recent publications on the advances and data concerning the use of rituximab in LN, to provide the available information and perform a critical analysis of the limited evidence supporting this information.

Methodology

We conducted a literature search in the MEDLINE and Cochrane databases using the MeSH terms “lupus nephritis/drug therapy” and “rituximab”. We each performed a separate search, using filters so that only those studies defined as “clinical trial”, “multicenter”, “randomized controlled” or “comparative” were retrieved. We also selected observational studies, meta-analyses and/or systematic reviews using search filters. The search in the MEDLINE database yielded 11 studies[10–20] involving humans published between 1 January 2000 and 30 May 2015. Of the 11, 3 were observational (2 prospective[11,12] and 1 retrospective[13]). The remaining 8 were clinical trials (7 were open-label[14–20] and only 1, the LUNAR study,[10] was randomized, parallel-group and placebo-controlled). We included those observational or experimental studies that involved LN patients—and those involving SLE patients in which a subgroup of LN patients was analyzed—and were designed to evaluate partial and complete remissions in response to treatment with rituximab. One of the open-label clinical trials was excluded because it included only 1 patient.[15] We obtained a Cochrane database review.[21] The bibliography of each of the selected studies was reviewed in search of other relevant articles; moreover, additional information was sought in the UpToDate™ database using the terms “nefritis lúpica” and “rituximab”. This additional search in the UpToDate™ database yielded no more studies of interest and the information was used as a reference resource for other sections of this review. The exclusion of the article by Fra et al.[15] left a total of 10 studies.

Rituximab in Observational Studies

The characteristics of the observational studies retrieved are summarized in Table 1.

In their retrospective study, Melander et al. included 20 patients who received rituximab as induction therapy for class IV and class V LN, with a follow-up of less than 12 months.[13] Remission was finally achieved in 12 patients (60%): 7 complete and 5 partial. Rituximab was administered as first-line treatment in only 2 patients. In this study, the normalization of the glomerular filtration rate was used as a criterion for complete remission (≥60 mL/min/1.73 m^2).

In 2010, Terrier et al.[12] published a prospective study in France, in which they analyzed the data of the French Autoimmunity and Rituximab Registry. This registry invites the hospitals of France to participate in order to analyze those patients with autoimmune diseases refractory to treatment who are receiving rituximab. In 42 patients with LN (class IV in the great majority), renal response was achieved in 23 of 31 patients with available data for this category. Of these 23 patients, 14 (45%) experienced a complete remission and 9 (29%), partial remission. Proteinuria was markedly reduced, although the serum creatinine level remained stable. However, as the registry is for SLE in general, it does not provide specific data