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Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: A systematic review

Tatiana Cobo-Ibáñez, MD, PhD[a,*], Estíbaliz Loza-Santamaría, MD[b], José María Pego-Reigosa, MD, PhD[c], Alejandro Olivé Marqués, MD, PhD[d], Íñigo Rúa-Figueroa, MD[e], Antonio Fernández-Nebro, MD, PhD[f], Rafael Cáliz Cáliz, MD[g], Francisco Javier López Longo, MD, PhD[h], Santiago Muñoz-Fernández, MD, PhD[a]

[a] *Rheumatology Department, Hospital Universitario Infanta Sofía, Paseo de Europa, 34, San Sebastián de los Reyes 28702, Madrid, Spain*
[b] *Institute for Musculoskeletal Health, Madrid, Spain*
[c] *Rheumatology Department, Vigo, Department, Instituto de Investigación Biomédica de Vigo (IBIV), Vigo, Spain*
[d] *Rheumatology Department, Hospital Universitario Germans Trías i Pujol, Badalona, Barcelona, Spain*
[e] *Rheumatology Department, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Spain*
[f] *Rheumatology Department, Hospital Regional Universitario de Málaga, Universidad de Málaga, Instituto de Investigación biomédica de Málaga (IBIMA), Málaga, Spain*
[g] *Rheumatology Department, Hospital General Universitario Virgen de las Nieves, Granada, Spain*
[h] *Rheumatology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

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ABSTRACT

Objective: To analyse the efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus (SLE).

Methods: We systematically searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials up to June 2013. The following were the selection criteria: (1) adult patients with SLE, (2) rituximab treatment, (3) placebo or active comparator, (4) outcome measures assessing efficacy and/or (5) safety. Meta-analysis, systematic literature reviews, randomised control trials (RCT), open clinical trials and cohort studies were included.

Independent extraction of articles by 2 authors using predefined data fields was performed. The quality of each study was graded using the Oxford Levels of Evidence and Jadad's scale.

Results: A total of 26 articles met our inclusion criteria: one RCT and its exploratory analysis, 2 open studies and 22 cohort studies, which analysed 1,231 patients. Overall, patients had active disease refractory to steroids and/or immunosuppressant drugs. Acceptable evidence suggested improvements in disease activity, arthritis, thrombocytopaenia, complement and anti-dsDNA, with a steroid-sparing effect. But relapses of disease were demonstrated too. Weak evidence suggested a response in anaemia, cutaneous and neuropsychiatric manifestations. Available evidence revealed few major adverse events. Studies had medium methodological quality and in general were applicable to current practice.

Conclusion: Rituximab has been shown to be safe and effective in the treatment of non-renal SLE, especially in terms of disease activity, immunologic parameters and steroid-sparing effect. However, it can only be recommended for organ-specific manifestations such as arthritis and thrombocytopaenia. High-quality studies are needed in order to consider the long-term effects of re-treatment on different organ-specific manifestations.

From the Systemic Autoimmune Diseases Study Group of the Spanish Society for Rheumatology (EAS-SER).

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* Corresponding author.
E-mail address: mtcoboiba@yahoo.es (T. Cobo-Ibáñez).

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with protean manifestations in multiple organ systems. Current medical practice includes glucocorticoids, antimalarials and immunosuppressant (ISS) drugs to reduce disease activity and prevent flares. However, these treatments are not enough to control the disease. Some patients have several manifestations simultaneously and need an additional treatment to control general disease activity. Furthermore, some patients may have refractory organ-specific manifestations, such as arthritis, or life-threatening situations, such as neurological involvement. Currently, off-label use of rituximab has been used as an alternative on the basis that several abnormalities in SLE B cell populations have been identified and play a central role in the pathogenesis of SLE. Some studies have stressed the efficacy of rituximab in the treatment of most manifestations, with many of these studies focusing on nephritis [1–4]. Previously, some systematic reviews tried to summarise the information concerning efficacy and safety of rituximab in the treatment of SLE [5,6], but the data on the outcomes did not discriminate between studies that focused on nephritis and those that did not. In addition, specific outcomes relating to non-renal manifestations were not evaluated. In order to recommend rituximab, it would be useful to identify a profile of patients who are most likely to benefit from its use, particularly considering the recent approval of belimumab, which shows non-renal non-severe manifestations and flare-prevention effects. Both biologic treatments are not exclusive; the same patient may need them at some point.

Thus, the aim of this article was to systematically review the available literature regarding the efficacy and the safety of rituximab in the treatment of non-renal manifestations of SLE.

Methods

This study was performed by experts from the Evidence-based Medicine Study Group and the Systemic Autoimmune Diseases Study Group of the Spanish Society of Rheumatology. Initially, we conducted a systematic review on the efficacy and the safety of biologic and non-biologic ISS drugs in the treatment of non-renal SLE. The data about non-biologic ISS drugs have been recently published [7]. Now, we present data on rituximab.

Search strategy

The studies were identified by sensitive search strategies in the main bibliographic databases: MEDLINE from 1961 to June 2013, EMBASE from 1980 to June 2013 and the Cochrane Central Register of Controlled Trials up to June 2013. An expert librarian (M.P.R.L.) checked the search strategies. Finally, a hand search was performed by reviewing the references of the included studies. Details about strategies are available in a supplementary file (Appendix 1).

Selection criteria

The studies retrieved by the above strategies were finally included if they met the following pre-established criteria: (1) adult patients diagnosed with SLE; (2) treatment with rituximab; (3) placebo or active comparator; (4) outcome measures assessing efficacy—non-renal manifestations, activity index scores, SLE flare, steroid-sparing effect, etc. and/or (5) outcome measures assessing safety—infections, malignancies, etc. Only meta-analyses, systematic literature reviews, randomised control trials (RCT), open clinical trials and cohort studies with at least 10 non-renal SLE patients were included.

Screening of studies, data collection and analysis

The titles and abstracts of the retrieved articles for the selection criteria were screened independently by 2 reviewers (T.C.I. and E.L.S.). They collected the data from the studies using ad hoc standard forms. All articles were selected in duplicate and independently. One of the reviewers (T.C.I.) entered the data from the forms into spreadsheets. In case of any discrepancy between the information of both reviewers, a consensus was reached by reading the original article. Articles with insufficient data or assessing anti-malarial drugs and non-biologic or biologic ISS drugs other than rituximab were excluded. We also excluded specific articles about lupus nephritis, cutaneous lupus erythematosus or paediatric SLE and basic scientific articles.

The quality of the studies was assessed using the Oxford CEBM "Levels of evidence" [8]. The Jadad scale was also used if the study was a RCT (Appendix 2) [9]. Because the study designs, participants, interventions and reported outcome measures varied, we focused on describing the studies in evidence tables, their results and qualitative synthesis rather than meta-analysis.

Results

The literature search produced 3410 articles, of which 186 underwent full review and 24 met the inclusion criteria. We identified 2 additional studies by hand search (Fig.). The evidence table including the population studied, interventions and outcomes with their definitions is available in Appendix 3. The excluded studies and reasons for exclusion are shown in Appendix 4.

The 26 studies included 1 RCT and its exploratory analysis [10,11], 2 open-label studies [12,13] and 22 cohort studies (15 prospective) [14–35], which analysed up to 1231 patients (Table 1 and Appendix 3). Most of the patients were women, with an age ranging from 15 to 84 years and with active disease refractory to glucocorticoids and/or ISS drugs. A total of four studies [10,17,26,31] only included patients with non-renal disease. Regarding therapies, 6 cohort studies [15,21–24,26] presented patients with severe disease on rituximab combined with IV cyclophosphamide, the rest were on rituximab as monotherapy. Although dosing and infusion regimens were variable, the two regimens that were most common were 375 mg/m^2/week for 4 weeks and 1 g of rituximab on days 1 and 15. In most studies, glucocorticoids and non-biologic ISS drugs were concomitant treatments. Follow-up ranged from 2 to 103 months, and adverse events were reported in 23 studies [10,12–17,19–26].

The main results are summarised in Tables 1 and 2. The level of evidence and the grade of recommendation are shown in Table 2.

Global disease activity

All but 3 cohort studies [18,30,32] reported disease activity outcomes measured with different scores or indexes (Table 1). One RCT that analysed rituximab in patients with active non-renal SLE found no clinical or statistically significant differences at 52 weeks, except in the subgroup of African–American/Hispanic patients who achieved more complete and partial responses than the placebo [10]. One open-label and 12 cohort studies [13,14,18,20–23,26–29,32,34] reported short-term (3–9 months) statistically significant improvement in disease activity (77.7–88.8% complete/partial remission or 64.2–90.9% complete/partial response). Long-term outcomes ($\geq$ 12 months) were reported in 1 open-label study and in 6 cohort studies [12,15,16,24,25,30,35]. In 3 of these cohorts [15,30,35], complete or partial response/remission rate was 70–100%. In the other 2 cohorts [16,24] that specifically assessed