Efficacy and Safety of Rituximab in the Management of Pediatric Systemic Lupus Erythematosus: A Systematic Review

Ines Mahmoud, PhD[1], Manel Jellouli, MD[2], Imen Boukhris, PhD[3], Rim Charfi, MD[4], Aicha Ben Tekaya, MD[1], Olfa Saidane, MD[1], Maryem Ferjani, MD[2], Yousra Hammi, MD[2], Sameh Trabelsi, PhD[4], Narjess Khalfallah, PhD[3], Rawdha Tekaya, PhD[1], Tahar Gargah, PhD[2], and Leila Abdelmoula, PhD[1]

Objectives To evaluate the efficacy and safety of rituximab for treating pediatric systemic lupus erythematosus (pSLE).

Study design We performed a systematic review to evaluate the efficacy and safety of rituximab in children with pSLE. Data from studies performed before July 2016 were collected from MEDLINE, the Cochrane Library, Scopus, and the International Rheumatic Disease Abstracts, with no language restrictions. Study eligibility criteria included clinical trials and observational studies with a minimal sample size of 5 patients, regarding treatment with rituximab in patients with refractory pSLE (aged <18 years at the time of diagnosis). Independent extraction of articles was performed by 2 investigators using predefined data fields.

Results Twelve case series met the criteria for data extraction for the systematic review with a good quality assessment according to an 18-criteria checklist using a modified Delphi method. Among them, 3 studies were multicenter and 3 were prospective. The total number of patients was 272. Studies collected patients with active disease refractory to steroids and immunosuppressant drugs. Refractory lupus nephritis was the most common indication (33%). Acceptable evidence suggested improvements in renal, neuropsychiatric and haematological manifestations, disease activity, complement and anti-double stranded Desoxy-Nucleo-Adenosine, with a steroid-sparing effect. However, there was poor evidence suggesting efficacy on arthralgia, photosensitivity, and mucocutaneous manifestations of SLE in children. An overall acceptable safety profile with few major adverse events was shown.

Conclusion Rituximab exhibited a satisfactory profile regarding efficacy and safety indicating that this agent is a promising therapy for pSLE and should be further investigated. *(J Pediatr 2017;187:213-9).*

The incidence of pediatric systemic lupus erythematosus (pSLE) is 0.3-0.9/100 000 children per year, with a prevalence of 3.3-8.8/100 000 children.[1] pSLE is associated with more severe and active disease compared with systemic lupus erythematosus (SLE) in adults. In particular, there is a higher incidence of renal and central nervous system involvement.[2,3] Immunosuppressive therapies are widely used but fail to show efficacy in severe forms of the disease.

B-lymphocyte function is a major component of SLE pathogenesis.[4,5] Rituximab (RTX) is a chimeric monoclonal IgG1 kappa antibody that binds specifically to the CD20 antigen and mediates B-cell depletion, thereby preventing the renewal of autoantibodies and antigen presentation by pathogenic B cells.[6,7] Recent reports have suggested the use of RTX for patients with SLE who are refractory to standard treatment approaches; however, RTX therapy has not been approved for this indication.[8] To understand and interpret the available evidence, we conducted a systematic review to evaluate the efficacy and safety of RTX therapy in children with pSLE.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was performed in the digital databases of MEDLINE, Scopus, Web of Knowledge, and the Cochrane Library. We also searched the electronic databases of the American Society of Rheumatology, the European League Against Rheumatic Disease, and the French Society of Rheumatology. We performed a hand search by reviewing the references of the included studies. We searched all databases from their earliest records up to July 2016. Keywords included terms and synonyms for RTX, lupus, and child.

LUNAR	Lupus Nephritis Assessment with Rituximab
pSLE	Pediatric systemic lupus erythematosus
RTX	Rituximab
SLE	Systemic lupus erythematosus

From the [1]Department of Rheumatology; [2]Department of Pediatric Nephrology; [3]Department of Internal Medicine, Charles Nicolle Hospital, Faculty of Medicine, Manar University, Tunis, Tunisia; and [4]Department of Clinical Pharmacology, National Centre of Pharmacovigilance, Faculty of Medicine, Manar University, Tunis, Tunisia

The authors declare no conflicts of interest.

0022-3476/$ - see front matter.
http://dx.doi.org10.1016/j.jpeds.2017.05.002

Selection Criteria

We included both clinical trials and observational studies of pediatric patients (aged <18 years) with SLE treated with RTX, published in full text or abstract. There was no language restriction. A minimum sample size of 5 patients was required for inclusion. Studies including both children and adults were excluded if the data for children could not be extracted separately.

Data Extraction

Two investigators reviewed titles and abstracts and then selected potential manuscripts for retrieval. The same investigators collected the data from the potential studies by applying the aforementioned selection criteria. A standardized data collection form was used to extract the following information: type of study and use of controls, number of patients, patient age, systemic involvement of SLE, dose and administration schedule of RTX, other medications, and outcome measures assessing the efficacy and/or safety and duration of response. The definition of efficacy for nonrenal manifestations included activity index scores, SLE flares, steroid-sparing effects, and effects on laboratory measures. Of the several definitions of primary outcome used, the most common was an improvement in clinical disease activity according to the SLE Disease Activity Index. Definitions of partial and complete remission used in the various studies are listed in **Table I** (available at www.jpeds.com). Safety records included reports of infections and malignancies.

Risk of Bias Assessment

We used an 18-criteria checklist developed by a panel of 7 Health Technology Assessment researchers using a modified Delphi method to perform a quality assessment on case series studies.[21] Checklist items included study objective, study population, interventions and cointerventions, outcome measures, and statistical analysis. Two investigators (I.M. and M.J.) rated each study working independently; any disagreements were resolved by consensus. The criterion for inclusion of a study was a score of ≥14 out of a possible 18.

Pooling of Data

Given the differences in study design, interventions, and reported outcome measures, a meta-analysis was deemed inappropriate, and we focused on describing the studies in evidence tables with their results and a qualitative synthesis.

Results

Our search of the databases yielded 549 citations, of which 12 studies[9-20] (with a total of 272 patients) met the inclusion criteria, including 10 complete articles and 2 abstracts (with 32 patients).[10,18] The **Figure** (available at www.jpeds.com) illustrates the literature selection process. All of the studies were case series and did not include a control group.

Quality Assessment

All of the studies clearly described an objective, patient inclusion/exclusion criteria, patient characteristics, and main findings (**Table II**). Likewise, all studies had clearly defined outcomes. Three studies were multicenter,[14,15,20] 3 studies collected patient data prospectively,[10,13,18] and 3 studies involved consecutive enrollment of patients.[11,13,18]

Epidemiologic Characteristics

British, American, and Canadian studies were predominant (a total of 162 patients; 60%).[9,13,15,17,19] The patients were mostly female (80%) and ranged in age from 6 to 28 years. The mean age at onset of SLE was reported in 6 studies and ranged from 7.8 to 12.5 years. The mean duration of disease was reported in 9 studies and ranged from 1.4 to 4.7 years. Regarding previous therapies, all of the patients had failed to respond to cyclophosphamide and mycophenolate mofetil, and most had failed to respond to at least 1 other immunosuppressive agent (ie, azathioprine, intravenous immunoglobulin, methotrexate, cyclosporine, tacrolimus, or thalidomide). The duration of follow-up ranged from 1 month to 36 months. Study characteristics are summarized in **Table III**.

Table II. Quality assessment of the studies according to the modified Delphi method

Studies	Objective clearly described	Inclusion/exclusion criteria clearly described	Multicenter study	Data collected prospectively	Patient characteristics clearly described	Outcomes clearly defined	Main findings clearly described
Willems et al (2006)[20]	Y	Y	Y	N	Y	Y	Y
Nwobi et al (2008)[17]	Y	Y	N	N	Y	Y	Y
Podolskaya et al (2008)[19]	Y	Y	N	N	Y	Y	Y
Jansson et al (2011)[14]	Y	Y	Y	N	Y	Y	Y
Su et al (2012)[10]*	Y	Y	NR	Y	Y	Y	Y
Pavon-Sanchez and Sánchez-Sánchez (2013)[16]	Y	Y	N	N	Y	Y	Y
Alexeeva et al (2013)[18]*	Y	Y	N	Y	Y	Y	Y
Lehman et al (2014)[13]	Y	Y	N	Y	Y	Y	Y
Ale'ed et al (2014)[12]	Y	Y	N	N	Y	Y	Y
Olfat et al (2015)[11]	Y	Y	N	N	Y	Y	Y
Tambralli et al (2015)[9]	Y	Y	N	N	Y	Y	Y
Watson et al (2015)[15]	Y	Y	Y	N	Y	Y	Y

N, no; *NR*, not reported; *Y*, yes.
*Abstract.