

RITUXIMAB TREATMENT FOR RHUPUS SYNDROME: A SYSTEMATIC LITERATURE REVIEW

S. Miladi, H. Ben Ayed, Y. Makhoulf, H. Boussaa, Z. Leith, K. Ben Abdelghani, A. Fazaa, A. Laatar

Rheumatology Department, Mongi Slim Hospital, Faculty of Medicine of Tunis, University Tunis El Manar – Tunis, Tunisia

Abstract. *Rhupus is a poorly described and underdiagnosed disease in which features of both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) appear in the same patient. Herein, we present a systematic literature review to analyze the clinical, laboratory and radiological data of all reported rhupus patients treated with rituximab (RTX). This systematic review followed the preferred reporting items for systematic reviews guidelines. Eligible articles were searched in Medline, Embase, and Cochrane Library. We analyzed cohort studies, case series and case reports. Four papers were finally selected for analysis. The studies were published between 2012 and 2022. Overall, 29 patients were included. All rhupus patients were previously treated with conventional Disease-Modifying Antirheumatic Drugs (DMARDs) and RTX was the first biologic DMARD prescribed in 22 patients. A significant reduction in the mean value of Disease-activity-score-28 (DAS28) from baseline to the end of follow-up was observed in all the studies. Mean DAS28 decreased from 5.65 to 3.65. The clinical activity of SLE was evaluated in 2 studies using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Overall, mean SLEDAI decreased from 6.05 at baseline to 2.66 at the end of follow-up. Based on the ultrasonographic (US) disease activity assessment performed in one study, US count scores progressively reduced, indicating that a US response was sustained after RTX treatment. Overall, only two severe adverse events were noted. In the light of this literature systematic review, RTX seems to be effective and safe in rhupus syndrome.*

Key words: systemic lupus erythematosus; rheumatoid arthritis; rituximab; biologics

INTRODUCTION

Rhupus or “rhupus syndrome” is commonly considered to feature the presence of symptoms of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in the same patient [1]. In 1971, Schur [2] used for the first time the term ‘rhupus’ to describe patients satisfying the criteria for both SLE and RA, without establishing whether this coexistence was a distinct immunoclinical entity or only the coincident presence of both conditions in the same patient. This condition is one of the uncommon and sporadically documented overlaps [1, 2]. Its prevalence has been estimated to be around 0.01% to 2% of patients with rheumatic diseases [3, 4], and women are most affected and account for 84% to 100% of reported patients [5-7]. Given the absence of specific criteria that describe this entity, it is challenging to identify such patients [2]. RA is the first diagnosis in two-thirds of patients, while the others are diagnosed either with SLE first or directly with rhupus [6-8]. The most reported clinical features of rhupus syndrome are erosive polyarthritis, rheumatoid nodules, malar rash, photosensitivity, alopecia, and the presence of constitutional symptoms. Renal and neurological involvement is rarely reported [4, 8]. The polyarticular, erosive, and seropositive inflammatory picture justifies the application of hydroxychloroquine, corticosteroids, and

methotrexate to control the articular inflammatory process and alleviate constitutional symptoms. Other medications that can be helpful, especially if there is evidence of renal involvement, are mycophenolate mofetil (MMF), and biologic therapy. All tumor necrosis factor- α (TNF- α) inhibitors have been linked to the onset of antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid antibodies (anti-dsDNA antibodies), and drug-induced lupus, including confirmed SLE renal disease [7]. In this context, some authors have discussed the potential effect of anti-CD20, as a promising alternative to TNF- α inhibitors [9-12]. In fact, rituximab (RTX), an anti-CD-20 chimeric monoclonal antibody, is validated for RA but its efficacy in SLE is debated because of the discordant results of some clinical trials and other open-label studies and cohorts [12-14].

Herein, we present a systematic literature review to analyze the clinical, laboratory and radiological data of all reported rhupus patients treated with RTX and to provide up-to-date information about the efficacy and safety of the anti-CD 20 therapy in rhupus.

All data analyzed were extracted from published studies. For the present paper, no ethical approval or written informed consent was required. The search strategy, literature selection, and data extraction were conducted by two investigators (SM and BAH) inde-

pendently, then discussed, and any disagreement was resolved by consensus. This systematic review was registered in PROSPERO: number 467634.

SEARCH STRATEGY

This systematic review followed the preferred reporting items for systematic reviews guidelines (PRISMA) [15]. Eligible articles were searched in Medline, Embase, and Cochrane Library. For PubMed, the search was carried out using a strategy employing the combination of the MeSH (Medical Subject Headings) terms "rhus", and "rituximab" or their synonyms (Box 1). For Embase and Cochrane Library, the previous terms were searched in the article title, abstract, or keywords. We selected relevant published articles in English, French, Italian and Spanish that included adult cases. We manually searched additional references in articles. Articles with incomplete information, pediatric cases and duplicate publications were excluded. We analyzed cohort studies, case series and case reports. If any study included overlapping data, the most comprehensive one was selected. After a deep analysis of titles and abstracts, articles unrelated to the inclusion criteria were excluded.

Box 1. Applied terms in the present systematic review

Synonyms of rhus syndrome	Synonyms of rituximab
"lupus AND erosive", "lupus AND rheumatoid arthritis AND overlap "	"CD20 Antibody", "rituximab CD20 Antibody", "Mabthera", "IDEC-C2B8 Antibody", "IDEC C2B8 Antibody", "IDEC-C2B8", "IDEC C2B8", "GP2013" and "Rituxan"

SELECTION CRITERIA

A comprehensive search was conducted from inception until August 30th 2023. The inclusion criteria for the present systematic review were:

1) Patients 18 years of age and older, with a diagnosis of rhus syndrome. We extracted the definition of rhus syndrome as it was proposed by the authors.

2) Patients treated with rituximab (RTX) with available data on disease outcomes before and after the RTX courses.

3) Comparison of rhus syndrome outcomes before and after RTX courses with or without a control group.

Exclusion criteria were: (1) rhus syndrome associated to other autoimmune diseases; (2) articles not in compliance with the systematic review purpose.

DATA EXTRACTION AND QUALITY ASSESSMENT

Extracted data from each study was evaluated independently by both investigators (SM and BAH). The extracted data included the main methodological characteristics of the articles: study data (year of publication, country, study design, number of included subjects, mean age of included subjects, inclusion and exclusion criteria, duration of the follow-up). Our main outcome was comparison of the rhus syndrome outcomes before and after RTX treatment (RA activity, SLE activity, drugs dosage variation). Furthermore, we identified potential biases of the cohort studies using JBI (Joanna Briggs Institute) critical appraisal for case series [16]. Only studies that met high quality belonged to our final selection (Supplement) [17].

Supplement: JBI Critical Appraisal Checklist for Case Series 1) Author_M. Piga Year_2013 Record Number Lupus 2013 22: 624

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	x	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	x	☐	☐	☐
Were valid methods used for identification of the condition for all participants included in the case series?	x	☐	☐	☐
Did the case series have consecutive inclusion of participants?	☐	x	☐	☐
Did the case series have complete inclusion of participants?	x	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	☐	☐	x	☐
Was there clear reporting of clinical information of the participants?	x	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	x	☐	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	x	☐	☐	☐
Was statistical analysis appropriate?	x	☐	☐	☐

Overall appraisal: Include x; Exclude ☐; Seek further info ☐

2) Author Andrade-Ortega Year 2013 Record Number Reumatol Clin. 2013;9(4):201-205

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	x	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	x	☐	☐	☐
Were valid methods used for identification of the condition for all participants included in the case series?	x	☐	☐	☐
Did the case series have consecutive inclusion of participants?	x	☐	☐	☐
Did the case series have complete inclusion of participants?	x	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	☐	☐	x	☐
Was there clear reporting of clinical information of the participants?	x	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	x	☐	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	x	☐	☐	☐
Was statistical analysis appropriate?	x	☐	☐	☐

Overall appraisal: Include x; Exclude ☐; Seek further info ☐

3) Author Rottenberg Year 2022 Record Number J Clin Rheumatol. 2022;28(8):e699-e702

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	x	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	x	☐	☐	☐
Were valid methods used for identification of the condition for all participants included in the case series?	x	☐	☐	☐
Did the case series have consecutive inclusion of participants?	x	☐	☐	☐

Did the case series have complete inclusion of participants?	x	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	☐	☐	x	☐
Was there clear reporting of clinical information of the participants?	x	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	☐	x	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	x	☐	☐	☐
Was statistical analysis appropriate?	☐	☐	x	☐

Overall appraisal: Include x; Exclude ☐; Seek further info ☐

4) Author Araújo Year 2013 Record Number Acta Reumatol Port. 2013;38:290-294

	Yes	No	Unclear	Not applicable
Were there clear criteria for inclusion in the case series?	x	☐	☐	☐
Was the condition measured in a standard, reliable way for all participants included in the case series?	x	☐	☐	☐
Were valid methods used for identification of the condition for all participants included in the case series?	x	☐	☐	☐
Did the case series have consecutive inclusion of participants?	x	☐	☐	☐
Did the case series have complete inclusion of participants?	x	☐	☐	☐
Was there clear reporting of the demographics of the participants in the study?	☐	☐	x	☐
Was there clear reporting of clinical information of the participants?	x	☐	☐	☐
Were the outcomes or follow up results of cases clearly reported?	x	☐	☐	☐
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	x	☐	☐	☐
Was statistical analysis appropriate?	☐	☐	x	☐

Overall appraisal: Include x; Exclude ☐; Seek further info ☐

The initial search yielded 26 papers. Overall, 4 papers were finally selected for analysis. The process of article selection is outlined in Figure 1.

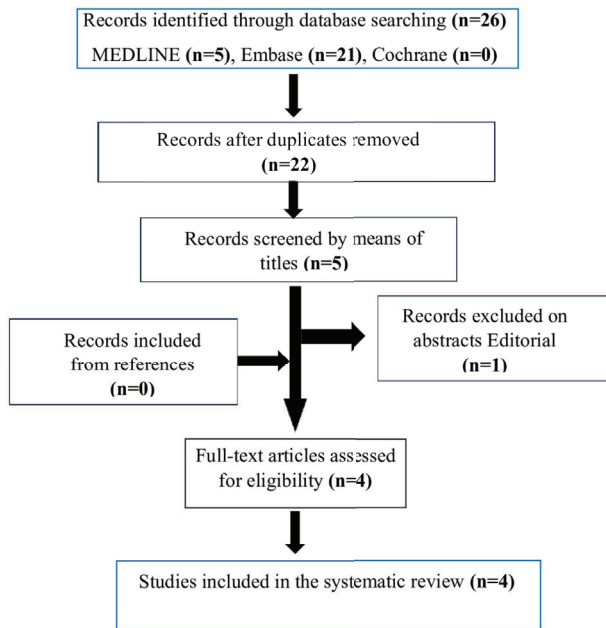


Fig. 1

CHARACTERISTICS OF THE STUDIES

The main characteristics of the 4 studies retained in this systematic review are represented in Table 1 [9-12].

The studies were published between 2012 and 2022 [10, 12] and were conducted in Portugal [9], France [10], Italy [11] and Mexico [12].

The applied designs were the prospective clinical study [12], the case series [9], the longitudinal pilot study [11] and the medical records review study [10].

The exclusion criteria were mentioned in only 2 studies [11, 12]: pregnancy or breastfeeding, a medical history of hepatitis, the necessity to use concomitantly another immunosuppressant or conventional DMARD (except hydroxychloroquine), an active infection at the time of the enrolment in the study [12] and the refusal to participate in the study [11].

CHARACTERISTICS OF THE PATIENTS

The main characteristics of the patients are represented in Table 2.

Overall, 29 patients were included and the sample sizes varied from 5 [9] to 9 [10, 12]. The mean age was mentioned in only 3 studies [9, 11, 12] and it was of 48.5 years with extremes ranging between 34 [11] and 80 years [9]. In the study of Rottenberg et al. [10], only the mean age at the diagnosis of rhus was mentioned and it was of 39.7 years (23-64).

Table 1. Main characteristics and results of the selected studies aiming to assess the efficacy of rituximab in patient with rhus

First author (ref)	Study design/ Characteristics of the population studied (mean age, gender)	*Inclusion/exclusion criteria	Disease activity assessment criteria	Duration of the follow-up period	Main outcomes	Conclusion of the authors
Andrade-Ortega et al. [12] 2012	A prospective, open clinical study including 9 patients/ 43 years (38-57), all females	* Patients ≥ 18 years of age with a diagnosis of rhus syndrome according to the criteria proposed by Simon et al. [22]. * Patients having moderate or strong joint activity (DAS28 ≥ 3.2)/ * The presence of pregnancy or breastfeeding. * A medical history of hepatitis. * The necessity to use concomitantly another immunosuppressant or another DMARD (except HCQ).	The main objective: A change in DAS28 at 6 months The secondary objectives: A change in SLEDAI at 6 months. Changes in DAS28 and SLEDAI during follow up and until the end of the evaluation. Steroid requirement.	24 months	A statically significant decrease in the mean DAS28 from 5.73 to 4.13 at 3 months and to 3.02 at 6 months. The improvement in mean DAS28 was maintained during the follow-up period (DAS28 of 3.04 at 12 months and 2.52 at 24 months) A statically significant decrease in the mean SLEDAI from 5 points at baseline to 2.56 at 3 months and 1.22 at 6 months. The improvement in the mean SLEDAI was maintained during the follow-up period (SLEDAI of 0.78 at 12 months and 0.22 at 24 months).	RTX seems to be effective both in joint manifestations, with significant reduction of DAS28, as well as in other manifestations of lupus, with improvement of MEX-SLEDAI. The clinical response was evident at 6 months but it started from 3 months of evaluation and was maintained in all patients during the follow-up with repeated infusions.

		*An active infection at the time of the enrolment in the study.				Prednisone dose was tapered from 11.66 mg/day to 4.72 at 6 months and to 1.11 mg/day at 24 months. In 8 patients, an increase in DAS28 activity was observed between 9 and 12 months so a second rituximab treatment was administered	RTX may be effective and safe in SRD other than RA.
Araújo F et al. [9] 2013 Portugal	Case series of 5 patients 54.2 years (37-80), all female	*Patients with rheupus syndrome diagnosis as it was defined by the authors: previous diagnosis of SLE with current erosive polyarthritis; previous diagnosis of RA with current clinical features of SLE; simultaneous clinical features of SLE and RA/	The 3-variable DA28 The 4-variable DA28 Drug dosage variation after RTX treatment	24 weeks		Significant decline in the mean 3-variable DAS 28 and in the mean 4-variable DAS 28. Significant reduction in mean standard treatment dosage (methotrexate, salazopyrine and prednisone)	
Piga et al. [11] 2013 Italy	Longitudinal pilot study including 6 patients/ 48.4 years (34-69), NM	*Patients suffering from rhupus, defined by fulfilment of criteria for both SLE (1982 ARA/ACR criteria) and RA (1987 ACR criteria), showing X-ray erosions and a score of DAS28 > 5.1 despite conventional DMARD treatment and a stable medication for at least 4 weeks prior to study enrolment/ Patients who refused to participate to the study	Clinical and laboratory assessment with calculation of the DAS28 and SLEDAI scores. US assessment (Sum of joints and tendons showing US synovial effusion, US synovial proliferation and PD signal, respectively). Radiographic assessment using the Sharp-van der Heijde scoring method	56 weeks		Progressive and significant decline in the mean SLEDAI, ESR-DAS28 and US count scores. No progression of the structural damage after 1 year of treatment of RTX.	RTX may be useful in severe active and refractory rhupus syndrome, with inhibition of structural damage and low rate of severe adverse events.
Rottenberg et al. [10] 2022 France	A 10-year medical records review study which identified 16 patients with rhupus syndrome, 9 of them were treated with RTX/ 39.7 years (23-64), NM	*Patients fulfilling 2010 ACR/EULAR and 2012 SLICC and/or 2019 ACR/EULAR classification criteria for RA and SLE, respectively.	NM	10 (4–13) years		Only 1 case of primary failure of RTX was noted, 8 patients responded to the treatment and 6 maintained their response (3 cases of secondary failure)	RTX seems to show efficacy in rhupus syndrome, with a majority of maintained responses. It could become an interesting approach in the future for the treatment of rhupus.

RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, RTX: rituximab, DAS28: 28-Disease activity score, SRD: Systemic rheumatic diseases, NM: Not mentioned, ACR: American college of rheumatology, ARA: American rheumatism association, DMARD: Disease-Modifying Antirheumatic Drugs, US assessment: Ultrasonographic assessment.

Table 2. Main characteristics and results of the selected studies aiming to assess the efficacy of rituximab in patient with rhus syndrome

Authors	Characteristics of the population studied (mean age, gender, mean disease duration)	* Inclusion/ *exclusion criteria	Reasons for RTX treatment	Previous treatment	RTX dosage	Duration of the follow-up period	Disease activity assessment criteria	Disease activity at baseline	Disease activity at the end of follow-up	Drug dosage variation at the end of follow-up	Safety
Andrade-Ortega et al. [12] 2012 Mexico	A prospective, open clinical study including 9 patients/ 43 years (38-57), all females, 10.03 years (1.8-22).	* Patients ≥ 18 years of age with a diagnosis of rhus syndrome according to the criteria proposed by Simon et al. [22]. *Patients with joint disease activity (DAS28 ≥ 3.2) *Pregnancy or breastfeeding. * A medical history of hepatitis. *The necessity to use concomitantly another immunosuppressant or another DMARD (except HCQ). *An active infection at the time of the enrolment in the study.	Moderate/severe joint disease activity (DAS28 ≥ 3.2) despite conventional DMARDs	MTX: 8/9 patients HCQ: 7/9 patients AZA: 3/9 patients MMF: 2/9 patients CYC: 1/9 patient SLZ: 7/9 patients	Two 1000 mg infusions 2 weeks apart	24 months	The main objective: A change in DAS28 at 6 months The secondary objectives: A change in SLEDAI at 6 months. Changes in DAS28 and SLEDAI during follow up and until the end of the evaluation. Steroid requirement	Mean DAS28: 5.73 Mean SLEDAI: 5	Mean DAS28 at 6 months: 3.02/ Mean DAS28 at 24 months: 2.52 Mean SLEDAI at 6 months: 1.22/ Mean SLEDAI at 24 months: 0.22	Prednisone dose was tapered from 11.66 mg/day to 4.72 at 6 months and to 1.11 mg/day at 24 months.	Infusion-related reaction: 2 cases Non-serious infectious events: 9 cases (lower urinary tract infections: 6 cases/ upper respiratory tract infections: 3 cases. Serious infectious: 1 case)
Araújo F et al. [9] 2013 Portugal	Case series of 5 patients/ 54.2 years (37-80), all females, 14 years (9-30).	* Patients with rhus syndrome diagnosis as it was defined by the authors: previous diagnosis of SLE with current erosive polyarthritis; previous diagnosis of RA with current clinical features of SLE; simultaneous clinical features of SLE and RA	Moderate (2 patients) and severe (3 patients) joint disease activity as indicated by the DAS28	- MTX: mean dose of 21 mg/week (all patients). HCQ: 400 mg/day (all patients). Prednisone: mean dosage of 8.5 mg/day (all patients). AZA: mean dosage of 125 mg/day (4 patients). Biologic DMARDs : 1 patient (Adalimumab, 40 mg every other week for 3 years, suspended for secondary failure).	Two 1000 mg infusions 2 weeks apart	24 weeks	The 3-variable DA28 The 4-variable DA28 Drug dosage variation after RTX treatment	Mean of the 3-variable DAS28: 4.89 Mean of the 4-variable DAS28: 5.23	Mean of the 3-variable DAS28: 3.31 Mean of the 4-variable DAS28: 3.48	Significant reduction in mean standard treatment dosage: - MTX: from 21 mg/week to 15 mg/week), -AZA: from 125 mg/day to 87.5 mg/day -Prednisone/ from 8.5 mg/day to 5 mg/day.	Severe infusion-related reaction near the end of the treatment in 1 patient. No reported infections in the follow-up period.

Piga et al. [11] 2013 Italy	Longitudinal pilot study including 6 patients/ 48.4 years (34-69) NM, LES: 12.5 years (1-27) and RA: 8.3 years (2-19)	*Patients suffering from rheupus, defined by fulfilment of criteria for both SLE (1982 ARA/ACR criteria) and RA (1987 ACR criteria), showing X-ray erosions and a score of DAS28 > 5.1 despite conventional DMARD treatment and DMARD treatment and a stable medication for at least 4 weeks prior to study enrolment/ *Patients who refused to participate to the study	A score of DAS28 > 5.1 despite conventional DMARD treatment	MTX: All patients HCQ: 5 patients AZA: 5 patients MMF: 1 patient	Two 1000 mg doses	56 weeks	Clinical and laboratory assessment with calculation of the DAS28 and SLEDAI scores. US assessment (Sum of joints and tendons showing US synovial effusion, US synovial proliferation and PD signal, respectively). Joints examined on US: the wrists, 2nd, 3rd and 4th MCPs, 2nd PIPs. Tendons: The wrist flexor and the wrist extensor tendons Radiographic assessment using SHS method	Mean TJC (68): 15 ± 1.8 Mean SJC (68): 7.7 ± 1.9 Mean VAS pain (100mm): 63 ± 6.2 Mean ESR (<15 mm): 26.1 ± 5.2 Mean CRP (0-0.5 mg/dl): 0.5 mg/dl Mean DAS28: 4.96 ± 0.36 Mean SLEDAI: 5.1 ± 0.7 US JC, SE (0-12): 3.3 ± 0.6 US JC, SP (0-12): 3.3 ± 0.6 US JC, P D (0-12): 2.5 ± 0.7 US TC, SE (0-26): 2.8 ± 2 US TC, SP (0-26): 2.8 ± 2 US TC, P D (0-26): 2.3 ± 2.1 Mean change in SHS: -0.5 (± 2.8)	NM	Adverse events: 2 patients Broncopneumonitis 2 months after baseline (1 patient) Mild infusional reaction resolved on reduction of infusion rate (1 patients)
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Rottenberg et al. [10] 2022 France	A 10-year medical records review study, which identified 16 patients with rhus syndrome, 9 of them were treated with RTX/ NM, NM	*Patients fulfilling 2010 ACR/EULAR and 2012 SLICC and/or 2019 ACR EULAR classification criteria for RA and SLE, respectively.	Joint activity	MTX: All patients HCQ: 8/9 patients AZA: 2/9 patients MMF: 1 patient CYC: 1 patient Thalidomide: 1 patient Other biologic DMARDs: 6 patients (Etanercept: 3 patients/ Infliximab: 1 patient/ Abatacept: 2 patients/ Anakinra: 1 patient/ Tocilizumab: 1 patient/ Adalimumab: 1 patient)	Two 1000 mg infusions 2 weeks apart	10 (4-13) years	NM	Median SJC (0-20): 9 Median ESR: 47.5 mm/h (4-60) Median DAS28: 5.45 (3.68-7)	NM	None
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RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, RTX: Rituximab, DAS28: 28-Disease Activity Score, SRD: systemic rheumatic diseases, NM: Not mentioned, ACR: American college of rheumatology, ARA: American rheumatism association, DMARD: Disease-Modifying Antirheumatic Drugs, US assessment: Ultrasonographic assessment, AZA: Azathioprine, MTX: Methotrexate, HCQ: Hydroxychloroquine, MMF: Mycophenolate mofetil, SJC: Swollen joint-count, TJC: Tender joint-count, VAS= Visual analogic scale, JC: joint-count, TC: Tender-count, SE: synovial effusion, SP: Synovial proliferation, PD: Power Doppler, SLEDAI: The Systemic Lupus Erythematosus Disease Activity Index, MCP: metacarpophalangeal joints, PIP: Proximal Interphalangeal joints, SHS: the Sharp-van der Heijde scoring, ESR: Erythrocyte sedimentation rate, CYC: Cyclophosphamide, SLZ: Sulfasalazine

The mean duration from the diagnosis of rhus to the enrolment in the study was mentioned in 2 studies [9, 12] and it was 10.03 years (1.8-22) in a study of Andrade-Ortega et al. [12] and 14 years (9-30) in the study of Araújo et al. [9]. In the study of Piga et al. [11], the mean SLE and RA duration were 12.5 years [1-27] and 8.3 years [2-19], respectively.

The diagnosis of rhus was made by fulfilment of criteria for both SLE (1982 American Rheumatism Association (ARA) [18]. The American College of Rheumatology (ACR) or 2012 Systemic Lupus International Collaborating Clinics (SLICC) [19] and/or 2019 ACR/ European Alliance of Associations for Rheumatology (EULAR) classification criteria) [20] and RA (1987 ACR or 2010 ACR/EULAR criteria (21) [10, 11], or the criteria proposed by Simon et al. [22] (symmetrical, erosive polyarthritis, signs and symptoms of SLE and anti-dsDNA and/or anti-Sm antibodies) (12), or as it was defined by the authors (9): previous diagnosis of SLE with current erosive polyarthritis; previous diagnosis of RA with current clinical features of SLE; simultaneous clinical features of SLE and RA.

Reasons for rituximab treatment:

Moderate or severe joint disease activity despite previous treatments was the main reason for treatment with RTX. The cut-off of the 28-Disease-activity-score (DAS28) [21] was 3.2 in 3 studies [9, 10, 12], and 5.1 in Piga et al. [11] study.

Regarding treatment modalities, all rhus patients were treated with conventional Disease-Modifying Antirheumatic Drugs (DMARDs) (Methotrexate (n = 28) [9-12], Hydroxychloroquine (n = 26) [9-12], Azathioprine (n = 14) [9-12], Sulfasalazine (n = 7) [12], Mycophenolate mofetil (n = 4) [10-12] cyclosporine (n = 1) [12], and thalidomide [10]. All patients received corticosteroids at some point in their disease, however, drug withdrawal or stably-dosed DMARDs was required for at least 6 months before inclusion [23]. Overall, RTX was the first biologic DMARD prescribed in 22 patients, prescribed in second line in 5 patients [9, 10] or fourth line in 2 patients [10].

The regimen used in all the studies was two 1000 mg infusions two weeks apart, with the possibility, in 3 studies, of subsequent cycles according to the disease activity and particularly articular flare [9, 10, 12]. Details of number of cycles in each study are summarized in Table 2.

DISEASE ACTIVITY ASSESSMENT CRITERIA

The DAS28 was used in all the studies to assess the joint disease activity. In the study of Araújo et al. [9], both the 3-variable [24] and the 4-variable

DA28 were used. An improvement in the disease activity was defined as a decrease of at least 0.6 of the DAS28 at 6 months in the study of Andrade-Ortega et al. [12]. In the study of Piga et al. [11], Power Doppler (PD) ultrasonographic (US) assessment at baseline and at weeks 14, 28 and 56 was performed to assess joint activity. Bilateral US examinations of the wrist, 2nd, 3rd and 4th metacarpophalangeal joints, 2nd proximal interphalangeal joint, hand and wrist flexor tendons and wrist extensor tendons were performed by the same experienced rheumatologist blinded to clinical, laboratory and radiographic findings [11]. The presence of tenosynovitis and synovitis was classified using the Outcome Measures in Rheumatology (OMERACT) preliminary definitions [25]. For synovial effusion (SE), synovial hypertrophy (SH) and the PD signal of each examined joint (0-12) or tendon (0-26), a dichotomous score (0=absent, 1 = present) was applied [11]. Overall counts for SE (0-38), SP (0-38) and for PD signal (0-38) were calculated at each visit (the sum of joints and tendons showing SE, SP and PD, respectively) [11]. The efficacy of RTX on the structural damage was assessed in only one study (11) using the Sharp-van der Heijde scoring method (SHS) [26].

The clinical activity of SLE was evaluated in 2 studies [11, 12], using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [27] and the Mexican version of the (MEX-SLEDAI) [28].

Conventional drugs and/or corticosteroids dosage variation after RTX treatment was evaluated in 2 studies [9, 12].

EFFICACY OF RITUXIMAB IN RHUPUS ACTIVITY

DAS28 variation from baseline to the end of follow-up was detailed in 3 studies and a significant reduction in mean DAS28 was observed in all: from 5.23 to 3.48 in the study of Araújo et al. [9], 5.98 to 4.96 in the study of Piga et al. [11] and 5.73 to 2.52 in the study of Andrade-Ortega et al. [12]. Thus, mean DAS28 decreased from 5.65 to 3.65 [9, 11, 12].

Overall, according to the DAS28 remission criteria (29), among the 19 patients who completed their first treatment courses [9, 11, 12], at the end of follow-up 11 patients achieved clinical remission ($\text{DAS28} < 2.6$), 2 had low disease activity ($2.6 \leq \text{DAS28} \leq 3.2$) and 6 maintained moderate or severe disease activity ($\text{DAS28} > 3.2$).

A significant reduction was also noted in mean SLEDAI in the studies of Andrade-Ortega et al. [12] (from 5 to 0.22) and Piga et al. (11) (from 7.1 to 5.1)

(Table 1). Overall, mean SLEDAI decreased from 6.05 to 2.66 [11, 12].

In the study of Rottenberg et al. [10], disease activity parameters after RTX were not mentioned but according to the authors, only one primary failure was noted, 8/9 patients responded to the treatment, and 5 maintained their response.

Based on the US disease activity assessment performed in the study of Piga et al. (11), US count scores progressively reduced, indicating that a US response was sustained after RTX treatment. In the same study (11), the mean change in total SHS was $-0.5 (\pm 2.8)$, indicating that there was no progression of structural damage after 1 year of treatment with RTX.

Regarding drugs dosage variation after RTX treatment, in the study of Araújo, mean methotrexate and azathioprine dosage were significantly reduced from 21 mg/week to 15 mg/week and from 125 mg/day to 87.5 mg/day, respectively. Mean prednisone dosage was tapered from 8.5 mg/day to 5 mg/day at 24 weeks in study of Araújo (9), and from 11.66 mg/day to 1.11 mg/day at 24 months in the study of Andrade-Ortega et al. (12). Details are summarized in table 2.

RITUXIMAB SAFETY

Overall, fifteen adverse events were noted: infusion-related reaction ($n = 4$), non-serious infections ($n = 10$) and serious-infections (requiring hospital management) ($n = 1$).

The infusion-related reaction was mild in 3 patients and severe in only one patient. (table 2).

To the best of our knowledge, this is the first systematic literature review focusing on the efficacy and safety of RTX in rhupus syndrome.

Four studies, published between 2012 and 2022, were selected for analysis.

Moderate or severe joint disease activity despite previous treatments was the main reason for treatment with RTX in all the studies. All authors highlighted that RTX was efficient in lowering the DAS28 or the SLEDAI and even US scores. Overall, only two severe adverse events were noted.

Rhupus is a poorly described and underdiagnosed disease in which features of both RA and SLE appear in the same patient, most often sequentially [6]. The most complete but also strictest and limiting reported definition is the fulfillment of the 2012 SLICC criteria for SLE and of the 2010 ACR/EULAR criteria for RA together with the presence of articular erosions, typical SLE-like organ involvement,

positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (anti-CCP), positive ANAs, and positive anti-dsDNA or anti-Sm antibodies [30]. Thus, the previous dichotomic image of SLE and RA having two distinct pathophysiological mechanisms is now being challenged by the data supporting the existence of common genetic risk factors for the two diseases [31], by the implication of the shared epitope in SLE arthritis [32] and by the first evidence of a Th1-polarized senescence-associated secretory phenotype in rhus patients [30].

Rhus is characterized by RA-like articular involvement, which is the main feature, associated with one or more lupus-like organ involvements [5, 6, 8]. When compared to the incidences in SLE patients, the incidences of hand arthritis, polyarthritis, symmetrical arthritis, joint swelling, morning stiffness, joint deformities, and rheumatoid nodules are significantly higher in rhus patients [5], while there is no significant difference in the counts between rhus and RA [8]. Moreover, the use of US and MRI in some studies has better characterized the already known RA-like pattern in rhus arthritis, which is different from the other subtypes of joints involvement in SLE patients. However, rhus patients have less frequent and less severe systemic involvement than SLE patients [5].

Regarding treatment modalities, since there is no validated therapeutic strategy, treatment is based on clinicians' experience and on the results of a few studies. Corticosteroids and conventional DMARDs are widely used to control arthritis and prevent joint damage in rhus patients [5, 8-12]. A few studies have focused on biologics, mostly typical RA agents such as TNF-alpha blockers [33], abatacept [34], tocilizumab [35], baricitinib [36], belimumab [37] and RTX [9-12]. In fact, RTX an anti-CD20 chimeric monoclonal antibody, was first approved for non-Hodgkin lymphoma in 1997 and was later licensed for treatment of RA in patients with inadequate response or intolerance to TNF-inhibitors [38]. RTX has been shown to induce and maintain clinical response and also to be protective against progression of joint destruction in RA patients [39, 40]. Many studies have demonstrated the clinical efficacy and safety of RTX in SLE [41-43]. Lupus nephritis (LN) is a serious complication of SLE and influences morbidity and mortality. Ramos-Casals et al. [42] analyzed seven observational studies regarding the use of rituximab in LN, in a total of 106 patients. There was a favorable response in 69% of them (half had a complete response, the other half had a partial response). Moreover, RTX was

successfully used in other refractory systemic rheumatic diseases such as inflammatory myopathies [44] [44], Sjögren's syndrome [45] and systemic sclerosis [46].

In the light of the results of the present review, RTX may be a safe, effective and steroid-sparing therapeutic option in rhus patients, with both a maintained clinical response [9-12] and a protection against progression of joint destruction [11]. In the study of Andrade-Ortega [12], a negative correlation between the clinical improvement assessed by DAS28 at 12 months and anti-CCP levels ($r = -0.794$, $p = 0.011$) was found. This result could be expected from the existing data on the positive association between the anti-CCP and joint damage in SLE [32, 47]. In fact, a positive association with erosive arthritis in SLE has been reported [32, 48, 49] and a statistical correlation has also been found with SLE-associated arthritis of all kinds (both erosive and nonerosive) [50]. Among rhus patients, the prevalence of anti-CCP antibodies is significantly higher than that in SLE patients [8, 50], and no difference [47] or decreased values [49] are found compared to those in RA.

CONCLUSION

Because of the lack of consensus on the definition of rhus and on its place in the spectrum of autoimmunity, there is no validated therapeutic strategy. In the light of this literature systematic review, RTX seems to be effective and safe in rhus syndrome. However, this evidence comes mainly from case series and studies with small sample sizes. Further studies in larger cohorts of patients are needed to confirm these preliminary data.

In conclusion, for the time being, the use of RTX in rhus patients should be restricted to patients with active disease that do not respond to conventional drugs.

KEY-MESSAGES:

- Since there is no validated therapeutic strategy, treatment of rhus syndrome is based on clinicians' experience and on the results of a few studies.
- Rituximab is validated for rheumatoid arthritis but its efficacy in systemic lupus erythematosus is debated because of the discordant results of some clinical trials.
- To the best of our knowledge, this is the first systematic literature review focusing on the efficacy and safety of anti-CD20 therapy in rhus syndrome.
- Rituximab may be a safe, effective and steroid-sparing therapeutic option in rhus patients.

Conflicts of interest: None.

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Yasmine Makhoul and Hiba Boussaa: Substantial contributions to the conception of the work.

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✉ Correspondence address:
Hiba Ben Ayed
telephone: +216 95 594 580
e-mail : benayedhiba3@gmail.com