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Review

The administration of low doses of rituximab followed by hydroxychloroquine, prednisone and low doses of mycophenolate mofetil is an effective therapy in Latin American patients with active systemic lupus erythematosus

Claudio Galarza-Maldonado [a], María R. Kourilovitch [a,b], Julio E. Molineros [c], Mario H. Cardiel [d], Luis Zurita [e], Nikolay F. Soroka [f], Viktor Y. Yagur [f], Natalia Doukh [g], Ricard Cervera [b,*]

[a] Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA), Hospital Monte Sinaí, Cuenca, Ecuador
[b] Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Catalonia, Spain
[c] Program of Arthritis and Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA
[d] Unidad de Investigación "Dr. Mario Alvizouri Muñoz", Hospital General "Dr. Miguel Silva", Morelia, Michuacán, México
[e] Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA), Clínica Alcívar, Guayaquil, Ecuador
[f] Department of Internal Medicine N2, Belarusian State Medical University, Minsk, Belarus
[g] Universidad de las Américas, Quito, Ecuador

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ABSTRACT

Background: In Latin America, the medical attention directed to systemic autoimmune diseases competes with a budget designed to fight poverty, lack of education, etc. In this context, the access to treatments recommended internationally are expensive and limited; therefore, research of methods that make these treatments cheaper is of paramount importance.
Objective: Our objective was to describe the 24-month clinical outcome of patients with active systemic lupus erythematosus (SLE) who received low doses of rituximab (RTX), followed by hydroxychloroquine (HCQ), prednisone and low doses of mycophenolate mofetil (MMF).
Methods: Forty-six patients with active SLE received 500 mg of RTX (together with 500 mg of methylprednisolone as a premedication) administered on two occasions 2 weeks apart, followed by HCQ (200–400 mg/day), prednisone and MMF (500–1000 mg/day) during a 24-month follow-up period. Clinical outcome was assessed using the MEX-SLE Disease Activity Index (MEX-SLEDAI) and serial serologic measurements. Remission was defined as MEX-SLEDAI scores 0–1, mild disease activity 2–5, moderate disease activity 6–9, severe 10–13, and very severe 14 or more.
Results: Disease activity decreased over time with treatment. At baseline, 19 (41.3%) patients had very severe, 16 (34.8%) severe, and 9 (19.6%) moderate disease activity. Improvement on disease activity was detected at 3 months, since 9 (19.6%) patients reached disease remission after this period of time and remission increased to 16 (34.8%) patients at 6 months, 19 (41.3%) at 1 year, and 23 (50%) at 2 years of follow-up ($p<0.0001$).
Conclusion: The administration of low doses of RTX followed by HCQ, prednisone and low doses of MMF is an effective therapy in Latin American patients with active SLE.

Contents

* Corresponding author. Department of Autoimmune Diseases, Hospital Clínic, Villarroel, 170, 08036-Barcelona, Catalonia, Spain. Tel.: +34 93 227 5774; fax: +34 93 227 17 07.
E-mail address: rcervera@clinic.ub.es (R. Cervera).

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune condition characterized by many diverse clinical manifestations, with different levels of disease activity and severity. Therapy should be addressed to obtain clinical remission; if this goal is not achieved, minimal disease activity can be an acceptable goal. The combination of several immunosuppressive and biological drugs has been an effective therapeutic strategy in patients with rheumatoid arthritis [1,2] and it would be worth to explore this strategy in SLE patients.

While corticosteroids remain the cornerstone drugs to control disease activity in SLE, other immunosuppressive agents are also used to treat several manifestations and, in many cases, they are prescribed for their steroid-sparing effect [3–5]. Rituximab (RTX), a chimeric monoclonal antibody against CD20 B cell receptor, has been approved by the Food and Drug Administration (FDA) for non-indolent lymphoma and also for rheumatoid arthritis who failed an anti-tumor necrosis factor (TNF) therapy. It has been enthusiastically used in SLE with positive clinical results in many case series [6–10]. However, two randomized clinical trials have been published recently that could not confirm those previous findings [11,12], but clinicians are reluctant to accept these results and several explanations have been postulated [13–15].

In Latin America, the medical attention directed to systemic autoimmune diseases, such as SLE, competes with a budget designed to fight poverty, lack of education, sanitation, etc. In this context, the access to treatments recommended internationally are expensive and limited; therefore, research of methods that make these treatments cheaper is of paramount importance to improve the quality of life of our patients. We think that by using smaller doses than those previously recommended, but in combination with other drugs, could help to improve our patients' health. We have been using RTX as part of a combination therapy for SLE since 2003. The objective of this study was to describe the 24-month clinical outcome of our patients with active SLE who received low doses of RTX, followed by hydroxychloroquine (HCQ), prednisone and low doses of mycophenolate mofetil (MMF).

2. Patients and methods

2.1. Patients

Forty-six patients, who fulfilled the American College of Rheumatology (ACR) classification criteria for SLE and had active disease, were invited to participate in this study. They received complete clinical information regarding therapeutic procedures and possible side effects. All of them accepted to participate following ethical guidelines. All the patients were seen and followed at the Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA) in Cuenca and Guayaquil, Ecuador.

2.2. Treatment regimen

2.2.1. Corticosteroids

All patients received a single intravenous methylprednisolone bolus of 500 mg before RTX infusion (pre-medication). Oral prednisone was maintained according to the clinical indication (initial doses 15–60 mg/day) and it was soon tapered according to clinical response.

2.2.2. RTX

Two infusions of 500 mg, 2 weeks apart, were administered to all subjects in an appropriate infusion unit following published guidelines [16].

2.2.3. MMF

It was prescribed as 1 g/day (in two separate 500 mg doses) in patients with lupus nephritis or 500 mg/day in non-renal SLE patients.

2.2.4. HCQ

All patients received 400 mg/day orally and it was tapered to 200 mg/day after 6 months and maintained during follow-up.

2.3. Outcome measures

They were obtained by a single observer in all patients at baseline and after 3, 6, 12, 18 and 24 months of treatment. Clinical and laboratory data were gathered to measure the MEX-SLE Disease Activity Index (MEX-SLEDAI) [17]. The original SLEDAI included 24 carefully defined variables and required laboratory confirmation in many cases. MEX-SLEDAI was reduced to the 10 main clinically defined variables and these were grouped by target organs. The main scoring differences between SLEDAI and MEX-SLEDAI are that seizures, psychosis, organic brain syndrome, cranial nerve involvement, and cerebrovascular accident were classified as neurological disorder. This category was assigned a weight of 8; visual and lupus headache were dropped since they are difficult to ascertain. Casts, hematuria and proteinuria were clustered together as renal disorder, with a value of 6; pyuria was dropped. Hemolysis was added and grouped with thrombocytopenia with a weight of 3. New rash, alopecia and mucous membrane lesions were clustered as mucocutaneous disorder with a value of 2 points. Pleurisy and pericarditis were put together with peritonitis and termed as serositis, with a value of 2. Lymphopenia was added and grouped with leucopenia with a value of 1. Low complement and increased DNA binding were dropped. The weights of vasculitis, arthritis and myositis were adjusted to preserve their relative contribution to the global score. In short, this clinical procedure measures disease activity following an organ and system approach, requires minimal routine laboratory data, has low cost and has been shown to have adequate reliability and validity in lupus patients [18]. MEX-SLEDAI is scored between 0 and 24. Although it is presented as an ordinal scale, arbitrary adjective definitions were created to facilitate communication of its scores. Remission was defined with scores 0–1, mild disease activity 2–5, moderate disease activity 6–9, severe 10–13, and very severe 14 or more.

All patients were clinically evaluated to look for side effects. Patients also had baseline laboratory evaluations including blood cell counts, erythrosedimentation rate, C reactive protein, urea, creatinine, urinalysis, 24-hour proteinuria, C3, C4 with nephelometry, antinuclear antibodies (ANA) using Hep2 cells and indirect immunofluorescence and a panel of antibodies including anti-dsDNA, anti-Ro, anti-La,

lupus anticoagulant and IgG and IgM anticardiolipin antibodies. Follow-up visits included blood cell counts, erythrosedimentation rate, C reactive protein, urea, creatinine, urinalysis, 24-hour proteinuria, and C3 and C4 determinations.

2.4. Statistical analysis

All data were captured in an Excel database and analyzed in SPSS version 17 and SAS. Descriptive statistics were used to present baseline characteristics in all patients. Inferential analysis was used to compare the effects of this combination therapy in disease activity. Baseline MEX-SLEDAI scores were compared to those at different periods of follow-up in a paired analysis using the Wilcoxon's non-parametric matched paired test. Statistical significance was assessed as a p value lower than 0.05.

3. Results

3.1. Effects on disease activity

Disease activity decreased over time with treatment (Table 1). At baseline, 19 (41.3%) patients had very severe, 16 (34.8%) severe, 9 (19.6%) moderate, and only 2 (4.3%) mild disease activity. No patient was on remission at baseline. Improvement on disease activity was detected at 3 months, since 9 (19.6%) patients reached disease remission after this period of time and remission increased to 16 (34.8%) patients at 6 months, 19 (41.3%) at 1 year, and 23 (50%) at 2 years of follow-up. The number of patients with very severe disease activity decreased from 19 (41.3%) subjects at baseline to 2 (4.4%) subjects after 2 years. All these comparisons reached statistical significance ($p<0.0001$).

3.2. Toxicity

The following infusion reactions were recorded: four patients had hypotension (defined as blood pressure <100/60 mmHg), another had tachycardia and one more had a skin rash. All of them were self-limited and none of them required the stoppage of medication. The following infections were detected during follow-up: one patient had acute bronchitis, one sinusitis, and one herpes zoster. No malignancies were detected.

3.3. Other outcomes

One patient died during follow-up because of renal failure. Persistent disease activity was seen in this patient. No autopsy study was performed. Another patient had chronic renal failure and is currently on hemodialysis.

4. Discussion

Therapy of SLE has different goals: (i) induction of response: aimed at rapidly controlling disease activity for prolonged periods; (ii) maintenance therapy: aimed at continuing remission and preventing flares; (iii) treatment of comorbidities: aimed at reducing the side effects of drugs employed to control activity and at controlling other associated conditions (i.e., hypertension, diabetes…) and minimizing damage. These aspects make the treatment of SLE complex and dependent on the use of combinations of drugs [19]. For these reasons, it is expected that the combination of different drugs can help to increase the effectiveness of the treatment and by using small doses of each of these drugs the risks of side effects will be reduced.

The doses of corticosteroids in patients with SLE should be given taking into account the activity of the disease, the risk factors and individual response. The doses should be lowered in case of remission or minimal activity. It is also important to take into consideration factors like hypertension, diabetes, peptic ulcers, recent fractures, glaucoma, infections, dislipidemia and concomitant medications such as non-steroidal anti-inflammatory drugs [20]. In our group of patients, the doses of corticosteroids that they were taking when they came to the consultation for the first time were maintained at the beginning but were soon tapered according to clinical response.

HCQ is used broadly in the treatment of SLE. Different studies have shown its effectiveness in preventing relapses, and reducing the risk of damage [21–23]. Tam et al. [24] have suggested that this drug could also modulate the risk of atherosclerosis which is increased in SLE patients. The “Grupo Latinoamericano para el Estudio del Lupus” (GLADEL) recently showed that antimalarial drugs have a protective effect on SLE survival in a group of 1,480 Latin America patients, possibly in a time-dependent manner [25]. The risk of thrombotic venous or arterial episodes in patients with SLE is significantly higher than that in the general population [26]. HCQ is a drug that can help to prevent these complications, as Jung et al. [27] have recently suggested.

MMF is a drug that has been used not only in patients with lupus nephritis but also to control other SLE manifestations [28]. In our group of patients, a dose of 500 mg/day of MMF was given to patients who had no renal involvement and 1000 mg/day to patients with lupus nephritis. According to a recent study, MMF seems to be as effective as cyclophosphamide in induction therapy for lupus nephritis [29]. Our results show that MMF in combination with other drugs is very effective in the treatment of these Latin American patients.

The effectiveness of RTX has been proposed based on experimental models of B cell depletion [30–34] and the action on T lymphocytes [35,36], as well as in different non-randomized clinical trials [37]. However, the EXPLORER and LUNAR trials failed to show the effectiveness of RTX to reach the primary endpoints proposed [11,12]. Nevertheless, based on personal experience of the UNERA team [6], and taking into account the different cases reported by many researchers around the world [38], we believe that RTX in combination with other drugs is an effective and secure therapy in patients with SLE.

In conclusion, the administration of low doses of RTX followed by HCQ, prednisone and low doses of MMF is an effective therapy in Latin American patients with active SLE. Therefore, we can confirm that the use of smaller doses than those previously recommended, but in combination with other drugs, can help to improve SLE patients' health in Latin America.

Table 1
Distribution of patients according to their MEX-SLEDAI score at baseline and after 3, 6, 12, 18 and 24 months of treatment with low doses of RTX followed by HCQ, prednisone and low doses of MMF.

Disease activity (MEX-SLEDAI score)	Baseline, No. (%)	3 months, No. (%)	6 months, No. (%)	12 months, No. (%)	18 months, No. (%)	24 months, No. (%)
Remission (0–1)	0 (0)	9 (19.6)	16 (34.8)	19 (41.3)	21 (45.7)	23 (50)
Mild (2–5)	2 (4.3)	1 (2.2)	2 (4.3)	2 (4.3)	2 (4.3)	3 (6.5)
Moderate (6–9)	9 (19.6)	27 (58.7)	27 (58.7)	21 (45.7)	21 (45.7)	18 (39.1)
Severe (10–13)	16 (34.8)	7 (15.2)	0 (0)	3 (6.5)	0 (0)	0 (0)
Very severe (≥14)	19 (41.3)	2 (4.3)	1 (2.2)	1 (2.2)	2 (4.3)	2 (4.3)
Total	46 (100)	46 (100)	46 (100)	46 (100)	46 (100)	46 (100)

Take-home messages

- In Latin America, the medical attention directed to systemic autoimmune diseases competes with a budget designed to fight poverty, lack of education, etc. Therefore, research of methods that make these treatments cheaper is of paramount importance.
- Low doses of rituximab (RTX), followed by hydroxychloroquine (HCQ), prednisone and low doses of mycophenolate mofetil (MMF) is a combination regimen that was administered to 46 patients with active systemic lupus erythematosus in Ecuador.
- Disease activity decreased over time with this combination regimen. At baseline, 19 (41.3%) patients had very severe, 16 (34.8%) severe, and 9 (19.6%) moderate disease activity. Nine (19.6%) patients reached disease remission after 3 months of therapy and remission increased to 16 (34.8%) patients at 6 months, 19 (41.3%) at 1 year and 23 (50%) at 2 years of follow-up.
- The administration of low doses of RTX followed by HCQ, prednisone and low doses of MMF is an effective therapy in Latin American patients with active SLE.
- The use of smaller doses than those previously recommended, but in combination with other drugs, can help to improve SLE patients' health in Latin America.

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