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Original article

## Treatment with rituximab for thrombocytopenia due to systemic lupus erythematosus

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### ABSTRACT

Some patients with thrombocytopenia due SLE fail to respond to conventional therapies. Rituximab has been reported to be an alternative for patient treatment.

**Objective:** To evaluate the response of thrombocytopenia due to Systemic Lupus Erythematosus to the use of Rituximab and patient relapse time at our hospital.

**Patients and methods:** We analyzed patients with SLE than received a 2 gram rituximab treatment for thrombocytopenia. We analyzed the rate of patients that achieved complete remission (CR), defined as a platelet count over 100 mil/mm<sup>3</sup>, partial remission (PR) described as platelets within 50-100 mil/mm<sup>3</sup> and no response (NR) if platelets remained unchanged and the time the remission was sustained.

**Results:** Sixteen treatments were applied to 13 patients, aged 28±9 years of age and SLE mean duration time of 68±44 months with a mean platelet count of 38±29 mil. In 14 treatments (87%) remission was achieved after 5±2 weeks where 2 patients (12.5%) were non respondent. One of them died due to a massive hemorrhage. The mean response time without relapse was 15.6±6 months. Follow up of three patients was not possible and 3 other died due to infections.

**Conclusions:** Rituximab is an alternative for treatment of thrombocytopenia due to Systemic Lupus Erythematosus.

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## Tratamiento con rituximab para la trombocitopenia secundaria a lupus eritematoso sistémico

### RESUMEN

#### Palabras clave:

Rituximab

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Trombocitopenia

En algunos casos la trombocitopenia secundaria a lupus eritematoso sistémico (LES) no responde al tratamiento convencional. En los últimos años se ha reportado que el rituximab es una alternativa para estos pacientes.

**Objetivo:** Evaluar la respuesta de la trombocitopenia (T) secundaria a LES con el uso de rituximab y determinar el tiempo que se mantiene el efecto libre de recaída.

**Material y métodos:** Se revisaron los expedientes de los pacientes con diagnóstico de LES con T que recibieron tratamiento con rituximab (2 g) para conocer la proporción de pacientes que lograron remisión completa (RC): definida como una cuenta plaquetaria > 100.000/mm<sup>3</sup>; remisión parcial (RP): cuenta plaquetaria entre 50.000 y 100.000/mm<sup>3</sup> y los no respondedores (NR); así como el tiempo que se mantiene el paciente sin recaída.

**Resultados:** Se aplicaron 16 tratamientos en 13 pacientes, en una paciente 3 y en otra 2 ciclos. Fueron 12 mujeres y 1 hombre con edad media de 28 ± 9 años y tiempo medio de duración del LES de 68 ± 44 meses, con una cuenta media plaquetaria de 38.000 ± 29.000. En 14 tratamientos (87%) se logró RC después de 5 ± 2 semanas y 2 pacientes (12.5%) fueron NR. Una de ellas murió por hemorragia masiva. El tiempo medio de respuesta sin recaída fue de 15.6 ± 6 meses. Tres pacientes perdieron el seguimiento y 3 murieron de infecciones.

**Conclusiones:** El rituximab es una alternativa de tratamiento en pacientes con T secundaria a LES.

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by affecting multiple organs. It is more common in young women of childbearing age and its prevalence varies depending on the population studied.<sup>1,2</sup>

Thrombocytopenia is a common manifestation in SLE, its prevalence ranging from 7% to 30% of patients, with the American College of Rheumatology (ACR)<sup>3</sup> defining it as a platelet count less of than 100,000/mm<sup>3</sup>. It can be severe in 5%-10% of cases. It is known as refractory thrombocytopenia when conventional treatment with steroids fails and a platelet count less than 30,000/mm<sup>3</sup> or clinical bleeding is seen, constituting a poor prognostic factor associated with elevated mortality.<sup>4,5</sup>

Steroids are still the first line of treatment, but many patients require immunosuppressive or other therapies to control the disease and prevent relapses.<sup>6-9</sup> However, some patients relapse, develop chronic refractory and/or complications due to disease or treatment that can lead to death.

In recent years it has been reported that the B cell plays an important role in the pathogenesis of SLE and represents a target for directing treatment.<sup>10,11</sup> Rituximab, a chimeric, anti-CD20, genetically engineered monoclonal antibody (human-mouse), targeting mature B cells, was initially approved for the treatment of Non-Hodgkins Lymphoma. In 1997, pilot studies appeared using rituximab in patients with autoimmune cytopenias,<sup>12,13</sup> and was later used in different autoimmune diseases including several of the clinical manifestations of SLE with encouraging results.<sup>14-16</sup>

In this study we retrospectively analyzed our experience with the use of rituximab in patients with SLE and thrombocytopenia to evaluate their response to treatment and to determine the time that the effect is maintained, free of relapse.

## Material and methods

Patients were obtained from the database of our Infusion Center at the High Specialty Medical Unit, Hospital de Especialidades No. 25 of the Mexican Social Security Institute; we selected patients with SLE who received rituximab between January and August 2008. We included patients who met the criteria for SLE according to ACR (1982) and that had thrombocytopenia, defined as a platelet count less than 100,000/mm<sup>3</sup>. Patients received a 2g infusion of rituximab in two divided doses (1 g/dosis) with 14 days between them. All patients were premedicated with dexamethasone 8 mg, paracetamol 1 g and 5 mg of diphenhydramine.

The following information was collected: age, gender, date of onset of SLE, primary indication for the use of rituximab pretreatment and a platelet count at one week, at one month, then every three months until the sixth month and then every year.

To evaluate the response we use the definitions proposed by the Mexican Hematology Group<sup>17</sup> which considers complete remission (CR) as a platelet count > 100,000/mm<sup>3</sup>, partial remission (PR) as a platelet count between 50 and 100,000/mm<sup>3</sup>, and non-responders (NR) when there was no change.

Relapse was defined as the time lag between CR and the onset of platelet descent, requiring adjustment of treatment according to clinical criteria set by the rheumatologist.

## Results

Sixteen treatments were applied to 13 patients, one patient received 3 cycles of therapy and another patient received two cycles of treatment. The primary reason for receiving rituximab was: thrombocytopenia in 10 patients and refractory lupus nephritis in

3. These 3 patients had their platelet count between 50,000 and 100,000/mm<sup>3</sup>.

There were 12 women and 1 man, with a mean age of 28±9 years, mean duration of SLE was 68±44 months and had an average platelet count of 38,000±29,000/mm<sup>3</sup> platelets. Patients had received an average of 3.8 prior treatments (2-6) and one patient had failed despite splenectomy (Table 1).

In 14 treatments (87%) CR was achieved and 2 patients (12.5%) were NR. The time to achieve remission was 5±2 weeks (2-12 weeks). Eight of the 10 patients with refractory thrombocytopenia achieved CR and two of them (patient 1 and 2) received more than one cycle of treatment with good response. The three patients who received treatment for control of nephritis as the primary indication achieved CR.

The time to relapse was 15.5±6 months (8-24) and follow-up time was 12±7 months (2-24 months) (Table 2).

Four patients died. Patient 9 died due to severe thrombocytopenia and airway bleeding five days after receiving rituximab. Patients 10 and 11 died of infection within the first 6 months of treatment. Another patient died during follow-up 18 months later with terminal renal failure, after receiving hemodialysis and with an added infection. Three patients were lost to follow up (Tables 3 and 4). During infusion, no patient developed a serious adverse event.

Here we present the description of six of the most relevant patients.

### Patient 1

A 20-year-old woman with SLE of 5 years since onset. Refractory thrombocytopenia treated with three drugs and had undergone splenectomy with no response. Underwent rituximab therapy with 13,400/mm<sup>3</sup> platelets achieving CR after 4 weeks. Remained recurrence free for 8 months. Considered as having a good response without relapse after 12 months. She received her third cycle of treatment and was followed for 3 months at the time of writing, without relapse.

### Patient 2

Twenty six-year-old woman diagnosed with SLE with three years since onset. She had presented polyneuropathy, serositis, rash, nephritis, arthritis and thrombocytopenia. She had received five previous medications for control and progressed to kidney failure with residual kidney function and frequent recurrence of thrombocytopenia. Received his first cycle of rituximab with 15,000/mm<sup>3</sup> platelets and achieved CR after 8 weeks. Received a second cycle due to 89,000/mm<sup>3</sup> platelets and went into remission for 16 months. At follow-up she has remained free of relapse after 23 months. No changes in renal function, and other manifestations were stable.

**Table 1**  
Demographic characteristics

Characteristic	
Gender F/M	12/1
Age, years	28±9
Duration SLE, months	68±44
Baseline platelets, mean*10 <sup>3</sup>	38±29

F indicates female; M, male; SLE, systemic lupus erythematosus.

**Table 2**  
Results in 16 treatments with rituximab

Response	n=16
Type of response, n (%)	
Complete remission	14 (87)
Partial remission	0
No response	2 (12.5)
Time to response, weeks	5±2
Time to relapse, months	15.5±6

**Table 3**  
Follow-up

Follow-up	n
Lost	3
Deaths	
Hemorrhage	1
Infection	3

**Table 4**  
Patients treated with rituximab and results

Case	Gender	Age	Indication	Prior treatment	Response	Relapse, months
1	F	20	T	4	CR	8
				4	CR	12
				4	CR	SR-3
2	F	26	T	5	CR	16
				5	CR	SR-23
3	F	26	T	4	CR	SR-15
4	F	46	T	3	CR	24
5	F	23	T	3	NR	-
6	F	23	T	5	CR	*
7	M	23	T	3	CR	*
8	F	21	T	3	CR	*
9	F	30	T	3	NR	-
10	F	51	T	4	CR	4
11	F	37	NL	6	CR	2
12	F	19	NL	5	CR	SR-18
13	F	38	NL	2	CR	SR-17

\* indicates patients lost; CR, complete remission; F, female; M, male; NR, no response; SR, no relapse; T, thrombocytopenia.

### Patient 5

Twenty three-year-old woman diagnosed with SLE 10 years before, with joint manifestations and hematologic affection. She had undergone three previous drug treatments without control of thrombocytopenia. She presented gingivorrhagia and was had a platelet count of 88.000/mm<sup>3</sup> when rituximab was started. There was no change in the platelet count and remained throughout the follow-up with platelet counts below 100.000 mm<sup>3</sup>.

### Patient 9

Thirty year old woman diagnosed with SLE four years before. She had arthritis, rash and refractory thrombocytopenia to three previous drugs. She came to the hospital with bruising, gingivorrhagia and 19.000/mm<sup>3</sup> platelets. She was treated with rituximab and died of respiratory tract bleeding five days after, with no change in the platelet count.

### Patient 10

Woman aged 51 with a diagnosis of SLE and hematological and joint affection of 14 years since onset. She had received four prior drugs with recurrence of thrombocytopenia. Temporary colostomy had complicated a case of diverticular disease two years earlier. She was seen with 6.630/mm<sup>3</sup> platelets and rituximab was initiated. Had CR after 8 weeks. Three months later, a rectal abscess complicated the clinical picture and she required a new colostomy; she progressed poorly and died a month later due to abdominal sepsis.

### Patient 11

Thirty seven year old female diagnosed with SLE 10 years before. She had arthritis, WHO type V lupus nephritis and thrombocytopenia

and had received six previous medications for control. Received rituximab for lupus activity, showing hypocomplementemia, increased proteinuria and thrombocytopenia. Entered the hospital due to activity and lower respiratory tract infection. Received intravenous antibiotics and steroids. Platelets count was recovered in four weeks, but had renal function deterioration and respiratory failure that required mechanical ventilation and intensive care. Had cardiorespiratory arrest and died with anoxoicemic encephalopathy 8 weeks after treatment with rituximab.

### Discussion

The treatment of thrombocytopenia, in some cases, constitutes a major challenge: 1) on the one hand there are patients with a good response to steroids but with frequent relapses, 2) the use of immunosuppressive therapies or other conditions sometimes has serious side effects that limit treatment and, 3) there are patients who develop refractory chronic illness and this factor is associated with morbidity and mortality.

For this reason, in recent years there has been a search for more effective drugs, and rituximab has been used with encouraging results.

We present our experience with the use of rituximab in the treatment of thrombocytopenia associated with SLE. In our group of 13 patients, 10 received rituximab for the treatment of refractory thrombocytopenia and, in 3 of them the primary indication being lupus nephritis.

The dose of rituximab used in published papers has varied and most of them have followed the recommendations of the Hematology groups (4 weekly infusions of 375 mg/m<sup>2</sup> BSA); in our hospital we decided to use the dose proposed for the treatment of rheumatoid arthritis, which was subsequently approved by the FDA. In open studies involving even a few patients, no differences were found with different treatment protocols. Clearly, controlled clinical trials are needed to define the dosage and recommendations for treatment with rituximab in patients with SLE.

We observed CR in 87% of cases and 12.5% were classified as NR.

García-Chavez,<sup>17</sup> treated patients with refractory autoimmune thrombocytopenia and reported a response rate of 78%, García Hernández<sup>18</sup> used rituximab in 13 patients with SLE and 5 of them had thrombocytopenia, reporting CR in 4/5 (80%) and partial response in the fifth (20%). Isenberg has published several clinical-serological studies in patients with different forms of active SLE and has reported improvement in the BILAG score, considering it a new treatment option, emphasizing the need for controlled studies.<sup>19</sup>

The high rate of CR we found is influenced by 3 patients who received rituximab as treatment for lupus nephritis and one patient who received a second cycle after relapse and had platelet counts between 50,000 and 100,000/mm<sup>3</sup>. However, although we did not consider these cases in the analysis, our remission rate was very good (75%), and similar to that reported in the literature.

The time to achieve remission was 5 weeks (2-12) and time to relapse was 15 months (8-24), similar to that reported, ranging from 4-32 weeks and 5-93 months respectively.<sup>20,21</sup>

We had four deaths, one of which was a few days after receiving rituximab, and which we believe was secondary to lupus activity that received delayed treatment; another died 18 months after treatment for secondary complications not associated with rituximab. Two patients died within the first six months of treatment (4 and 2 months respectively), a patient due to lupus activity associated with respiratory infection and the other with complicated diverticular disease; in these cases we cannot determine the influence of the application of rituximab. We believe that these were patients with severe disease and poor prognosis per se. We have no study of B cells,

important for correlation with treatment response and to analyze the immunological conditions of these two deaths.

Isenberg and others have reported that there is B-cell depletion in peripheral blood after administration of rituximab, and this is associated with clinical and serological improvement. This depletion is maintained for 3-11 months, although in some patients it lasted for some years. Association was also found between disease relapse and the recovery of peripheral blood B cells.<sup>22,23</sup>

We have no data on anti-dsDNA, or on C3, C4, which would have been of interest to search for an association to treatment response. Isenberg's serological data improved with depletion of B cells. Looney, however, reported improvement of the disease (SLAM) without changes in anti-DNA antibodies or complement.<sup>24</sup> These differences may be due to many factors, perhaps most importantly the fact that these were open studies with uncontrolled variables that may have affected the results.

We conclude that rituximab is an alternative in the treatment of patients with thrombocytopenia secondary to SLE, and prospective studies are needed to define the dosage and recommendations for management.

## Disclosures

The authors have no disclosures to make.

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