Original article

Efficacy and safety of rituximab in the treatment of primary antiphospholipid syndrome: Analysis of 24 cases from the bibliography review

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ABSTRACT

Background and objective: Antiphospholipid syndrome (APS) is characterised by the presence of antiphospholipid antibodies (aPL) and thrombotic and/or obstetric manifestations. Patients without another associated autoimmune disease are considered to have primary APS. Some patients develop thrombosis recurrence despite anticoagulant treatment and some clinical features do not respond to standard therapy. Rituximab may be an alternative in these cases. We review the published scientific evidence on the use of rituximab in the treatment of primary APS.

Patients and methods: Description of a case and review of the literature with descriptive analysis of the demographic, clinical, and immunologic features, treatment and outcome of patients.

Results: We identified 24 patients (15 women [62.5%]), with a mean age of 37.0 ± 13.4 years. The reasons for the use of rituximab were thrombocytopenia (41.7%), skin involvement (33.3%), neurologic and heart valve involvement (12.5%), hemolytic anaemia (8.3%) and pulmonary and renal involvement (4.2%). Lupus anticoagulant was present in 72.7% of the cases, the IgG and IgM isotypes of anticardiolipin antibodies in 75 and 50%, respectively, and the anti-β2GPI (IgG and IgM) antibodies in 80% of the patients. Thirteen (54.1%) patients received two doses of 1000 mg of rituximab fortnightly, 10 (41.7%) four doses of 375 mg/m² weekly and 1 (4.2%) eight doses of 375 mg/m² weekly. Eleven (45.8%) patients presented a complete clinical response, seven (29.2%) a partial response and six (25%) did not respond to rituximab. Four patients with clinical improvement presented with aPL titer decrease and in one patient, aPL levels did not change. In one patient without clinical response, aPL remained positive. A clinical-immunologic dissociation existed in two additional cases.

Conclusions: The results obtained suggest a possible potential benefit of rituximab in the treatment of some clinical manifestations of primary APS such as thrombocytopenia, skin and heart valve involvement.

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Eficacia y seguridad de rituximab en el tratamiento del síndrome antifosfolípido primario: análisis de 24 casos a partir de la revisión de la bibliografía

RESUMEN

Fundamento y objetivo: El síndrome antifosfolípido (SAF) se caracteriza por la presencia de anticuerpos antifosfolípido (AAF) y complicaciones trombóticas y/o obstétricas. Cuando no se asocia a ninguna otra enfermedad autoinmunaria recibe el nombre de SAF primario. En algunas ocasiones, el tratamiento antitrombótico no es suficiente para evitar la recurrencia trombótica, y algunas manifestaciones clínicas no responden al tratamiento estándar. Rituximab puede ser una alternativa en estos casos. Nuestro objetivo fue revisar la evidencia científica publicada del uso de rituximab en el tratamiento del SAF primario.

Palabras clave:
Rituximab
Síndrome antifosfolípido
Síndrome antifosfolípido primario
Thrombocytopenia
Valvulopatía

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Introduction

Antiphospholipid syndrome (APS) is characterised by the association of thrombosis and/or obstetric morbidity with the persistent presence of plasma circulating antiphospholipid antibodies (APLA), such as lupus anticogulant (LA), antiphospholipid antibodies (ACA) and/or antibodies targeted against specific proteins, such as β2-glucoprotein I (β2GPI).1 The most frequent clinical manifestation is deep venous thrombosis (DVT), while cerebrovascular accident (CVA) is the most prevalent manifestation of arterial thrombosis. Fetal losses (early and late), prematurity and preeclampsia are the most frequent obstetric manifestations.

When APS appears in patients who have no baseline disease, it is called primary APS. Systemic lupus erythematosus (SLE) is the autoimmune disease with which it is most frequently associated.

The treatment of thrombotic APS is based on the control of vascular risk factors, acetylsalicylic acid as primary thromboprophylaxis and long-term anticoagulant treatment as secondary thromboprophylaxis.

There is a series of manifestations not included in the qualifying criteria, such as thrombocytopenia or valvular involvement, the specific treatment of which is unknown; moreover, despite anticoagulant treatment, a group of patients shows thrombotic recurrence. In these cases, various alternative therapeutic strategies have been proposed, among them, rituximab. This is a human chimeric monoclonal antibody with activity against protein CD20 found in naive, mature and memory B lymphocytes. In the context of autoimmune diseases, the only indication approved by medicine regulatory agencies is rheumatoid arthritis refractory to drugs that modify the disease or anti-tumour necrosis factor α agents.

Two prospective, randomised, double blind studies were unable to show the efficacy of rituximab in patients with moderate SLE or with lupus nephropathy. Nonetheless, evidence obtained from observational studies supports the role of rituximab in the treatment of patients with serious or refractory lupus.

There is limited experience related to the use of rituximab in the treatment of APS compared to other autoimmune diseases. In cases of primary APS, it is merely anecdotic. A review from 2008 included 6 cases of primary APS, 6 cases of APS associated with SLE and one case of catastrophic APS treated with rituximab. A recent Phase II study has demonstrated its safety and efficacy in the treatment of some clinical manifestations not included in APS qualifying criteria.

The goal of the present study is to carry out a review of the scientific evidence available about the use of rituximab in primary APS. In addition, a case of primary APS treated with rituximab is described.

Patients and method

Data collection

A bibliographic search was carried out from the PubMed MEDLINE database up to May 2013 to identify all published cases of primary APS that received rituximab. The key words used were antiphospholipid syndrome and rituximab. Limitations on language and study design were not established, including isolated cases, case series, cohorts and controlled studies.

Articles describing patients with primary APS who received treatment with rituximab were included. The bibliography of the articles included was reviewed to obtain the entire number of cases. Articles written as reviews and those that describe patients with SLE or other associated autoimmune diseases or catastrophic APS were excluded from the study.

From the articles included, if available, the following data was gathered: demographics, clinical and laboratory data, APLAs and their titre, lymphocytes CD19+ count before and after treatment, previous and concomitant treatments, the line of treatment and dose of rituximab, clinical progress and blood tests, follow-up time, and adverse effects of the treatment. The definition of complete or partial response is described in each article. All the data was entered into a database designed for the study.

As the determination of APLAs in the different studies was made using different commercial tests, the results make reference to their maintenance, negativization or positivization before and after treatment with rituximab.

The results of continuous variables have been presented as means ± standard deviation (SD), and those of categorical variables as percentages.

Results

Clinical case

A 49-year old female patient with primary APS was diagnosed due to a foetal death during the fourth month of gestation and right pontine ischaemic CVA. The APLAs profile showed double positivity (IgG isotype ACA and LA). Moreover, she had experienced epilepsy during adolescence and autoimmune thrombocytopenia previous to APS diagnosis, which was refractory to corticosteroids and required a splenectomy. Subsequently, she had followed
treatment with prednisone 12.5 mg/day, azathioprine 100 mg/day, acenocumarol, calcium, vitamin D and pravastatin.

Her normal platelet counts were around $40 \times 10^9/l$. To perform the splenectomy and a uterine prolapse hysterectomy, she received intravenous immunoglobulin (IVIG) as prevention at doses of 25 mg per day for 5 days, without a significant increase in the number of platelets.

During the following months, the patient required 3 hospital admissions due to bleeding diathesis that coincided with a worsening of thrombocytopenia, up to $17 \times 10^9/l$, which did not respond to the increase in the corticosteroids dose or to new IVIG administration. Finally, treatment with rituximab 375 mg/m² weekly for 4 weeks was initiated, with no incidence or adverse effects. At the time of rituximab administration, ACAs were negative but the LA continued to be positive. The number of platelets after the first dose of the drug was $9 \times 10^9/l$, and after the third dose $24 \times 10^9/l$. Once treatment was completed, platelets remained around 15-18 $\times 10^9/l$ for the following 12 months, increasing to $45 \times 10^9/l$ at 18 months of follow-up. In successive check-ups, the values always remained over $50 \times 10^9/l$, and at 96 months follow-up the values were $78 \times 10^9/l$. From a clinical standpoint, she has not experienced ecchymosis or macroscopic haemorrhage again, and with the oral anticoagulant treatment she has never had a thrombotic recurrence. The corticosteroid dose was reduced to discontinuation at 36 month treatment with rituximab. The ACAs, which were negative before the administration of rituximab, have remained the same during follow-up. The LA, which was present at the beginning of the treatment with rituximab, was negative 60 months after administration of this drug and has remained negative to date.

Patients

The bibliographic search identified 83 articles that exhibited the above-mentioned conditions. Of those, based on a reading of the abstracts, 34 were discarded because they did not adjust to the screening criteria (lacking reference to APS treatment with rituximab). Using a more thorough analysis of the remaining 49 articles, the 32 cases that included APS treated with rituximab were selected, ruling out 17 of them which were reviews without case descriptions (n = 15) or cases that did not receive treatment with rituximab (n = 2) (Fig. 1). Finally, 32 articles with 47 cases of APS treated with rituximab were identified but 15 articles were discarded due to the inclusion of cases only related to associated APS, and 5 that, despite the inclusion of primary APS cases, fulfilled the criteria corresponding to catastrophic APS, which is a disease variation excluded from this review. Of the 12 articles selected, only one was a controlled study, while the rest were case series or descriptions of isolated cases.

General characteristics and previous manifestations

Finally, 24 patients with primary APS treated with rituximab were identified. Of these, one is the case described in this study, 12 are isolated published cases and 11 are part of the study that assessed the safety and efficiency of rituximab in the treatment of some manifestations not included in APS qualifying criteria (RITAPs). The main demographic, clinical and analytical characteristics of patients with primary APS are described in Table 1.

In 4 patients (16.7%), the clinical symptoms that triggered treatment with rituximab appeared at the beginning of the disease. Thirteen patients (54.2%) had previously experienced thrombotic complications, 3 (12.5%) had had obstetric complications and 4 patients (16.7%) had had both of these. In 2 patients the onset of primary APS satisfied catastrophic APS criteria.

Indications and doses of rituximab and concomitant drugs

The general indications for the use of rituximab are described in Table 1 and reported specifically for each patient in Table 2. The most frequent clinical indications were thrombocytopenia with haemorrhagic diathesis in 10 (41.7%) patients and skin involvement in 8 (33.3%). Skin involvement accounted for 6 cases of skin ulcerations/necrosis and 4 cases of livedo reticularis/livedoid vasculitis (in 2 patients, both types of injuries coexisted). Neurological involvement was the cause of treatment in 3 (12.5%) patients, in the form of cognitive deterioration. Three patients (12.5%) had cardiac valvular involvement, with data available for 2 of them, one with aortic vegetation and mitral valve thickening and the other with mitral valve thickening. In 2 (8.3%) patients, the treatment indication was thrombotic complications, one case of temporary CVA despite correct anticoagulant treatment and a patient with bilateral thrombosis of the cerebral venous sigmoid sinuses, with secondary bilateral papilledema. Two (8.3%) patients had symptomatic

![Table 1](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>9/15 (35.5/62.5)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>37.0 ± 13.4</td>
</tr>
<tr>
<td>Previous diagnosis of primary APS</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Previous clinical manifestations</td>
<td>17 (70.8)</td>
</tr>
<tr>
<td>Obstetric morbidity</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Indications for the use of rituximab</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Cardiac valvular involvement</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Serious haemolytic anaemia</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Laboratory data</td>
<td>8/11 (72.7)</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>9/12 (75.0)</td>
</tr>
<tr>
<td>ACA IgG</td>
<td>10/12 (50.0)</td>
</tr>
<tr>
<td>Anti-β2GPI IgG</td>
<td>12/15 (80.0)</td>
</tr>
<tr>
<td>Anti-β2GPI IgM</td>
<td>14/15 (93.3)</td>
</tr>
</tbody>
</table>

ACAs: anticoagulant antibodies; anti-β2GPI: antibodies anti-β2-glucoprotein I; SD: standard deviation; M: male.

a Defined as $<100 \times 10^9/l$ platelets.
b Defined as $<7.0$ g/l haemoglobin.
autoimmune haemolytic anaemia with haemoglobin values of 2.8 and 6.3 g/l, one of them associated with thrombocytopenia (Evans’s syndrome). Pulmonary involvement, in the form of alveolar haemorrhage and haemoptysis, and renal involvement, in nephrotic syndrome and acute renal failure, were present in one patient (4.2%) each.

Table 3 describes the administration guidelines for rituximab, the drugs previously used, and the concomitant treatment. In 7 (29.2%) patients, rituximab was part of the first line of treatment, 2 cases of skin involvement (one of them had previously responded to rituximab 6 months before), 2 cases of cardiac valvular involvement, 2 cases of thrombotic involvement and one case of cognitive alteration. Out of the remaining patients, it was administered as a second line treatment in 11 (45.8%), and in the remaining 6 (25%), it was administered after at least 2 previous lines of treatment.

The most frequently used guideline was the administration of 2 doses of 1000 mg fortnightly in 13 (54.1%) patients. Of these, 11 were part of the RITAPS study and received 1000 mg of oral paracetamol, 50 mg of oral dipyridamole and 100 mg of intravenous methylprednisolone about 30-60 minutes before each infusion, as per protocol. The twelfth patient received 500 mg of intravenous methylprednisolone the day before each infusion. Only one patient (4.2%) received 8 weekly doses of 375 mg/m² and the remaining 10 (41.7%) received 4 weekly doses of 375 mg/m². Of the last patients, 2 received supplementary doses. One of them received 2 monthly doses of 375 mg/m², as per the protocol used in mixed cryoglobulinaemia, and the other one received 2 doses of 1000 mg fortnightly for 3 months, due to the increase in the ACAs titres of IgG and IgM isotypes, even if they did not show symptoms. Likewise, one patient treated with 4 weekly doses of 375 mg/m² received coadjuvant methylprednisolone.

As treatments previous to the indication that triggered the use of rituximab, 4 (16.7%) patients (2 with skin involvement, one with cognitive alteration and another with haemolytic anaemia) received only corticosteroids treatment. One (4.2%) patient with thrombocytopenia and cognitive alteration received corticosteroids jointly with anti-D gammaglobulin, and another patient (4.2%), with thrombocytopenia and cardiac valvular involvement, received antagonists of the thrombopoietin receptor jointly with corticosteroids. Five (20.8%) patients received corticosteroids and IVIG before rituximab. Of these, 4 had thrombocytopenia (one of them with concomitant cognitive involvement and another one with haemolytic anaemia, who received cyclophosphamide associated to rituximab), and the fifth had ulcerative skin involvement. Apart from the use of corticosteroids and IVIG, one (4.2%) patient also received treatment with azathioprine due to refractory thrombocytopenia. In one (4.2%) patient with skin and renal involvement, plasma exchange was the preferred treatment before rituximab. The 4 remaining cases (16.7%), in which rituximab was not the first line of treatment, received different immunosuppressants. The case of pulmonary involvement was treated with prednisone, azathioprine, methylprednisolone, IVIG, cyclophosphamide and plasma exchange. Three cases of thrombocytopenia received prednisone, azathioprine, methylprednisolone, IVIG, cyclosporine A, vincristine and cyclophosphamide in one of them, plasma exchange, IVIG, cyclophosphamide, vincristine, dexamethasone and azathioprine in another, and corticosteroids, vincristine, IVIG and cyclophosphamide in the third.

As antithrombotic treatment, 13 (54.2%) patients received antiagulant medication, 4 (16.7%) antiaggregation and 4 (16.7%) a combination of both. One case was under treatment with oral prednisone and tacrolimus due to a previous renal transplant.

Clinical response to rituximab and follow-up

The progress of patients based on the clinical manifestations that triggered the use of rituximab and the follow-up period are described in Table 2. The mean follow-up was 72.0 ± 71.7 weeks (interval 24-356 weeks).

Overall, and in line with the criteria of the authors of each article, 13 (54.2%) patients achieved a complete clinical response with the treatment with rituximab. In detail, there were 4 patients with skin involvement in the form of necrosis, livedoid vasculitis and/or pyoderma gangrenosum, who presented total resolution of the injuries. Of these, one experienced clinical recurrence with the same involvement during week 36 of follow-up. Another patient with temporary CVA also experienced a complete response despite the anticoagulant treatment without new thrombotic symptoms.
during follow-up, and as did one case of renal involvement and normalisation of urine protein values. The resolution of sigmoid sinus thrombosis with recovery of visual acuity in one patient, the resolution of cognitive alteration in another case, and the increase in the number of platelets > 150 × 10^9/l in 3 patients with thrombocytopenia are other cases of complete clinical response. Two cases of cardiac valvular involvement corresponding to the study by Erkan et al. stand out: no changes were observed on completion of the 52 weeks of the study follow-up, but both cases achieved complete resolution in weeks 82 and 120, respectively.

Seven (29.2%) patients showed partial response to rituximab treatment. Four of them, with thrombocytopenia, maintained a platelet count between 50 and 150 × 10^9/l, y 2, with haemolytic anaemia and haemoglobin values between 9 and 12 g/l. A patient with skin involvement in the form of pyoderma gangrenosum experienced partial improvement of his injuries. Finally, the patient with alveolar haemorrhage and serious haemoptysis experienced a partial response, without any new episodes of diffuse alveolar haemorrhage but with episodes of mild haemoptysis.

Four (16.7%) patients did not experience any significant change with administration of the treatment. There were 3 cases of thrombocytopenia in which, after treatment, platelets remained under 50 × 10^9/l, and one case of cognitive alteration.

The response percentage based on treatment indication was highly varied. Complete response was 100% in the 2 cases treated due to thrombotic complications, while in the case of skin involvement 5 (62.5%) patients had a complete response and 3 (37.5%) a partial clinical response. There was high variability in the neurologic involvement response: one (33.3%) case with complete response, another (33.3%) with partial response and a third (33.3%) without response. In the long-term follow-up of the 3 cases with cardiac valvular involvement, one (33.3%) patient did not respond and 2 (66.7%) showed complete response. The only case with pulmonary involvement showed partial response and the patient with renal involvement showed complete response. The 2 patients with haemolytic anaemia experienced a partial response (100%), and in the case of thrombocytopenia, 3 (30%) patients experienced a complete response, 4 (40%) a partial response, and the other 3 (30%) did not show a significant response.

**Behaviour of antiphospholipid antibodies with rituximab**

The evolution of APLAs before and after rituximab is described in Table 4. The titration of APLAs at the time of rituximab treatment has only been obtained from data derived from different studies in 11 out of the 24 patients for LA, 12 for ACA IgG and 11 for ACA IgM, and only in 5 patients for anti-β2GPI. Before rituximab administration, LA was positive in 8 (72.7%) patients, ACA IgG in 9 (75%) and ACA IgM in 5 (45.4%). The positivity for anti-β2GPI IgG and IgM was confirmed in 4 (80%) of the 5 patients who were determined to have it.

Data on APLAs behaviour after rituximab administration was available for only 9 patients. A first case with negative APLAs and complete clinical response (skin necrosis) did not show variations in the values. The patient with pulmonary involvement had positive APLAs (LA, ACA and anti-β2GPI) from its beginning as catastrophic APS 12 months before; 6 months after the episode, anti-β2GPI normalised but ACAs had substantially increased. One case with previous positivity for LA and isotypes IgC of ACA and anti-β2GPI (since the onset of baseline symptoms, 9 years ago) received rituximab for the treatment of refractory thrombocytopenia, with complete clinical response and decrease in the APLAs titres, without achieving negativization during the 42 weeks of follow-up. The positivity of ACAs in the case with renal involvement experienced a decrease (ACAs IgM become negative) during the first 15 months of follow-up; subsequently, the titres increased without a clinical translation, thus, rituximab treatment was repeated and negativization of both isotypes was achieved 10 days after completion. Despite the anticoagulant treatment, the patient with thrombotic involvement had elevated and persistent ACA IgG titres.
which remained elevated after the treatment and a good clinical response. In the patient with thrombocytopenia and haemolytic anaemia who showed anti-β2GPI IgG and IgM, the partial response was accompanied by its negativization at 4 months. In one case of refractory thrombocytopenia, LA and ACA IgG and IgM remained positive. One patient with positivity for LA and the 2 isotypes of ACA and anti-β2GPI received rituximab as treatment for thrombocytopenia; before the treatment, IgM isotypes decreased without a substantial increase in the platelets. Upon completion of the treatment, anti-β2GPI IgG and IgM and ACA IgM became negative; 6 months after treatment, anti-β2GPI was positive again and the ACA IgM remained negative. In the case described, in spite of having recorded positivity before ACA IgM, ACAs were negative when rituximab was administered and remained like that during the follow-up. The LA, which was present at the beginning of the treatment with rituximab, became negative 60 months later and has remained negative to date.

**CD19+ lymphocyte count before and after treatment with rituximab**

This information was available for only 2 out of the 24 patients. The first case showed a complete clinical response and CD19+ lymphocytes decreased from 13.7% of the total amount of lymphocytes to 0.1% 2 weeks after the first dose of rituximab, to 0.0% 2 weeks after the second dose. The second case had no significant clinical response, the initial CD19+ lymphocyte count was 591 × 10^9/l and followed an erratic behaviour after the administration of the different rituximab doses. They initially decreased (204 × 10^9/l after the first dose and 160 × 10^9/l after the second one), and later increased (405 × 10^9/l after the third dose, 223 × 10^9/l after the fourth dose of rituximab and 280 × 10^9/l 6 months after the completion of the treatment).

A similar count was also carried out among the 11 patients of the RITAPS study, but the result is described as a mean ± SD, which also includes the rest of the patients (n = 8) that were part of the study and did not satisfy the qualifying APS criteria, so we cannot analyse their progress.

**Adverse effects of rituximab treatment**

Unfortunately, we cannot analyse the side effects of the treatment in the 11 patients of the RITAPS study because they are described jointly with the rest of the patients (n = 8) that are part of the study and did not satisfy the qualifying APS criteria. Of the remaining 13 patients with primary APS treated with rituximab, only one case with adverse effects after administration is described, which consists of 2 hospital admissions due to transient neutropenia and pneumonia, respectively.

**Discussion**

Rituximab, used as the first choice drug in one third of the patients, showed a good clinical response in the cases of thrombotic complications, skin and cardiac valvular involvement and, to a lesser extent, in the cases of haemolytic anaemia and thrombocytopenia. Its role in the variation of APLAs titres is more controversial.

The pathogenic role of APLAs has been demonstrated in animal models, where their presence increases the creation of thrombi in arterial and venous circulation. Moreover, there is evidence on the role of B lymphocytes as being responsible for the production of these autoantibodies. The subpopulation of B lymphocytes expressing CD5 in their surface is associated with the presence of APLAs. In this sense, no studies have been published about the depletion of B lymphocytes with drugs such as rituximab in animal models of APS. However, 2 studies have analysed the modulating treatment of B lymphocytes in murine APS models and, a third study has focused on blocking costimulating signals, such as antigen-4 associated to cytotoxic T cell.

Without a randomised clinical trial to support it, the evidence on rituximab efficiency in primary APS is based on descriptions of cases and case series described in the medical literature. In the previous published review, Erre et al. analysed 12 patients with APS treated with rituximab, of whom 6 had primary APS (all of them are included in our review). In these patients, an improvement or resolution of all cases of thrombocytopenia was confirmed (5 patients), along with an improvement in cerebral vasculopathy in one patient, recovery of haemolytic anaemia in 2 cases and only one thrombotic recurrence as DVT at 36 months of follow-up (8 patients).

The effect of rituximab on the APLAs and the clinical response is controversial. Several authors have described how, in patients with APS treated with rituximab, there is a close correlation between the decrease in the APLAs titres and the correction of thrombocytopenia, or the prevention of new onsets of thrombosis. In this sense, the lack of clinical response and the maintenance of elevated APLAs titres have also been related, which could be considered a therapeutic failure of rituximab. On the other hand, there are also descriptions of patients in whose cases, despite a good clinical response, APLAs titration was not modified. In the recent clinical trial conducted by Erkan et al. on the safety and efficacy of rituximab in the treatment
of manifestations not included in APS qualifying criteria, it is stated that this drug can be effective in the control of some manifestations without identifying substantial changes in APLAs titres. The scarce number of patients with APLAs determination after the treatment in this review prevents us from drawing definite conclusions on the matter, but it mainly seems to be a correlation between the clinical response and a decrease in the titration of all or part of the APLAs.

In the 2 cases where the CD19+ lymphocyte count is described, the results in relation to the clinical response are suspicious. In one case there was a correlation between lymphocyte depletion and complete clinical response13, while in the other case the absence of clinical response coincided with oscillating CD19+ lymphocyte count.

Based on the results obtained from this review, a potential benefit of rituximab could be proposed in the treatment of refractory cases of primary APS or at least, in the treatment of some of its clinical manifestations. Of these, thrombocytopenia has been the most frequent indication in the use of rituximab, with a variable response interval of: 30% complete response, 40% partial response and 30% with no significant improvement. This finding is compatible with, or even improves, the response rates of rituximab in patients with idiopathic thrombocytopenic purpura27. Skin involvement, which is the second most frequent indication, also seems to have a very good response (62.5% complete response and 37.5% partial response). Despite the scarce number of patients (2 cases), a very good response has also been observed in the cases of thrombosis (100% complete response) and in the long-term follow-up of cardiac valvular involvement (66.7% resolutions). However, with the current evidence, rituximab has demonstrated little efficacy in cases of APS and cognitive deterioration28.

The present study has some limitations, such as its retrospective character and the great heterogeneity of rituximab prescription criteria and the different administration guidelines, follow-up periods and response assessment both in clinical and serological terms. The following should also be noted: the reduced number of patients identified and the impossibility of obtaining all the data in each case, the potential screening bias based on which the trend is to publish only those cases with satisfactory results, and the coexistence of other immunosuppressive drugs in the treatment, which makes it difficult to establish the real role of rituximab in these patients. Moreover, all the reviewed articles, except for one, are isolated cases or case series.

The multifactorial aetiology of thrombosis in patients with APLA and the partial knowledge of the mechanisms by which these induce thrombosis and other clinical manifestations are the main barriers for the development of new drugs to treat APS. However, it is possible for the antithrombotic therapeutic approach to be replaced in the future by an immunomodulation approach more centred on the pathogenic mechanisms and not on the APLAs effect29.

Despite all the above-mentioned limitations, the data obtained in this study proves a potential benefit of rituximab in the treatment of some of the clinical manifestations of primary APS, such as thrombocytopenia and skin involvement. The association between clinical changes and the variations in APLAs titres is yet to be analysed. In this sense, randomised clinical trials should be developed to establish the real role of rituximab in the treatment of primary APS. Given the difficulties entailed in the performance of such a study, clinicians must be encouraged to share their experience in this field.

Conflict of interest

The authors declare that there are no conflicts of interest.

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