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

Isaac Pons[a], Gerard Espinosa[b,*], Ricard Cervera[b]

[a] Unidad de Enfermedades Autoinmunes Sistémicas, Servicio de Medicina Interna, Hospital d'Igualada, Igualada, Barcelona, Spain
[b] Servicio de Enfermedades Autoinmunes Sistémicas, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain

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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/m$^2$ weekly and 1 (4.2%) eight doses of 375 mg/m$^2$ 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.


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

*Palabras clave:*
Rituximab
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Síndrome antifosfolipídico primario
Trombocitopenia
Valvulopatía

RESUMEN

*Fundamento y objetivo:* El síndrome antifosfolipídico (SAF) se caracteriza por la presencia de anticuerpos antifosfolipídicos (AAF) y complicaciones trombóticas y/o obstétricas. Cuando no se asocia a ninguna otra enfermedad autoinmunitaria 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.

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* Corresponding author.
*E-mail address:* gespino@clinic.cat (G. Espinosa).

*Pacientes y métodos:* Descripción de un caso propio y revisión de la literatura médica con análisis descriptivo de las características demográficas, clínicas, analíticas, terapéuticas y evolutivas de los pacientes incluidos.
*Resultados:* Se han identificado 24 pacientes (15 mujeres [62,5%]), con una edad media (DE) de 37,0 (13,4) años. Las indicaciones de uso de rituximab fueron trombocitopenia (41,7%), afectación cutánea (33,3%), afectación neurológica y valvular cardíaca (12,5%), anaemia hemolítica (8,3%) y afectación pulmonar y renal (4,2%). El anticoagulante lúpico fue positivo en el 72,7% de los casos, los isotipos IgG e IgM de los anticuerpos anticardiolipina en el 75 y 50%, respectivamente, y los anticuerpos anti-β2GPI (IgG e IgM) en el 80%. Trece (54,1%) pacientes recibieron 2 dosis quincenales de 1.000 mg de rituximab, 10 (41,7%) 4 dosis semanales de 375 mg/m$^2$, y uno (4,2%) 8 dosis semanales de 375 mg/m$^2$. Once (45,8%) pacientes presentaron una respuesta clínica completa, 7 (29,2%) una respuesta parcial y 6 (25%) no experimentaron ningún cambio sustancial. Cuatro pacientes con mejoría clínica presentaron una reducción en el título de los AAF, y en uno, los valores no cambiaron. Un paciente sin respuesta clínica los mantuvo positivos. Existió una disociación clínico-analítica en un par de casos.
*Conclusiones:* Los datos obtenidos evidencian un posible beneficio potencial de rituximab en el tratamiento de alguna de las manifestaciones clínicas del SAF primario, como la trombocitopenia, la afectación cutánea y la afectación valvular cardíaca.


## 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 anticoagulant (LA), anticardiolipin 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. Foetal losses (early and late), prematurity and preeclampsia are the most frequent obstetric manifestations[2].

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 thromboprofilaxis and long-term anticoagulant treatment as secondary thromboprofilaxis[3].

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[4]. 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[5].

Two prospective, randomised, double blind studies were unable to show the efficacy of rituximab in patients with moderate SLE[6] or with lupus nephropathy[7]. Nonetheless, evidence obtained from observational studies supports the role of rituximab in the treatment of patients with serious or refractory lupus[8].

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[9–19]. 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[20]. A recent Phase II study has demonstrated its safety and efficacy in the treatment of some clinical manifestations not included in APS qualifying criteria[21].

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