Rituximab for refractory manifestations of the antiphospholipid syndrome: a multicentre Israeli experience

N. Agmon-Levin[1,2], M. Berman[3], L. Harel[2,4], M. Lidar[2,5], T. Drori[2,6], S. Hajyahia[1,2], D. Paran[2,3]

[1]Clinical Immunology, Angioedema and Allergy Unit, Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel; [2]Sackler School of Medicine, Tel-Aviv University, Israel; [3]Department of Rheumatology, Tel Aviv Medical Center, Israel; [4]Paediatric Rheumatology Unit, Schneider Children's Medical Center, Petah Tikva, Israel; [5]Rheumatology Unit, Center for Autoimmune Diseases; [6]Department of Neurology, Sheba Medical Center, Tel Hashomer, Israel.

Abstract

Objective

The clinical manifestations of the antiphospholipid syndrome (APS) are heterogeneous and related to anti-phospholipid antibodies (aPL). There is some evidence that B cells are involved in the pathogenesis of this condition. Thus the ability of rituximab (RTX) to deplete B cells makes it an appealing potential therapy for refractory antiphospholipid syndrome (APS). Real world data on RTX treatment of APS are still lacking. This study was conducted to report outcomes of RTX administration in the treatment of different aspects of APS.

Methods

This is a retrospective case series study on APS patients from 3 medical centres in Israel who were treated with RTX during 2010–2019 for refractory manifestations of APS including diffuse alveolar haemorrhage, recurrent thrombosis, cytopenia, neurological and skin manifestations. Medical records were reviewed regarding the clinical indication for RTX treatment, concomitant medications, RTX protocol, aPL status and response to treatment. Outcomes were defined as complete response if full resolution of the "indicated manifestation" was achieved and maintained for at least 12 months, partial response or no response.

Results

We identified 40 APS patients who were treated with RTX for refractory manifestations of this condition, of whom, 24 patients (60%) were female with a mean age of 40 years, and 31 patients (78%) were diagnosed with primary APS. A favourable response to RTX was documented in 32 patients (80%) including a complete response in 22 patients (55%). Response to RTX treatment was associated with a rituximab protocol of 375mg/m^2 x 4 compared to a fixed dose of 1000 mg x2 (100% vs. 65%; p=0.01). Complete response was associated with a decrease in aPL titres within 4–6 months post treatment, whereas no significant change in aPL titres was observed in patients with partial or no response.

Conclusion

Consistent with previous small case series, we report a good therapeutic response to RTX in patients with difficult to treat manifestations of APS. In this cohort, treatment protocols were associated with outcomes. Although further studies are required to verify our observations, our data support a plausible role for B cell depletion in refractory APS.

Key words

anti phospholipid syndrome, rituximab, systemic lupus erythematosus, diffuse alveolar haemorrhage, thrombocytopenia

*Agmon-Levin Nancy, PhD**
*Mark Berman, MD**
Liora Harel MD
Merav Lidar, MD
Tali Drori, MD
Soad Hajyahia, MD
Daphna Paran, MD

**These authors contributed equally.*

Please address correspondence to:
Nancy Agmon-Levin,
Clinical Immunology,
Angioedema and Allergy Unit,
The Zabludowicz Center for Autoimmune Diseases,
Sheba Medical Center,
52621 Tel Hashomer, Israel
E-mail:
nancy.agmon-levin@sheba.health.gov.il

Received on June 14, 2020; accepted in revised form on September 7, 2020.

Competing interests: none declared.

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder clinically characterised by thrombosis and/or obstetric morbidity, in the presence of serum antiphospholipid antibodies (aPL), obtained on two occasions, at least 3 months apart. Additionally, a myriad of non-criteria manifestations are common in APS (1). Both criteria and non-criteria manifestations, are mediated *via* a number of complex pathogenic mechanisms, most of which are driven by aPL. These autoantibodies, although necessary, are not sufficient for thrombosis, and a prerequisite second-hit has been proposed. Namely, an additional trigger such as infection, endothelial injury, inflammation, medications (*i.e.* oestrogen-containing pills), surgery or immobility, is required to promote clot formation (2, 3). On the other hand, various APS manifestations are linked with aPL induced inflammatory non-thrombotic effects (4). The most studied mechanism of aPL pathogenicity is the one associated with the β2-glycoprotein-I (β2GPI). This circulating apolipoprotein normally binds to phospholipids on endothelial cells (EC) and has a protective function against oxidative stress-induced cell injury. Anti- β2GPI antibodies fix β2GPI in an open conformation and form the anti β2GPI-β2GPI complex. The latter is able to induce inflammation and/or clotting via binding to a variety of receptors (*e.g.* Toll-like receptors 2 and 4, annexin A2 and GP1ba) on different cell types (*i.e.* ECs, monocytes, trophoblasts and platelets) that trigger intracellular signalling and inflammatory responses (5). Traditionally, treatment of APS focuses on antithrombotic strategies, which are less effective for the microvascular and non-thrombotic manifestations of the disease (6).

B cells play important roles in the pathophysiology of autoimmunity and particularly the APS. These roles include the production of autoantibodies and cytokines, antigen presentation and co-stimulation of T cells. Rituximab is an anti-CD20 monoclonal antibody, used for B cell depletion in a range of haematologic, rheumatologic and immune-mediated conditions. The ability of rituximab to deplete B cells and attenuate B cell effects makes it an appealing potential therapy for the APS. However, the available data on the dose and treatment regimen of rituximab, and its effects on APS manifestations is currently inconclusive. A number of small observational studies, case series and one non-randomised pilot study provided some evidence of beneficial effects of rituximab for APS and particularly for the catastrophic variant of disease (cAPS), whereas other reports did not confirm these results (6-11). Notably, in the open-label phase II, non-randomised pilot study, rituximab was administered to 19 APS patients with non-criteria manifestations. In this study, the largest so far, variable responses to treatment were reported with approximately half of the patients experiencing a partial or complete response (12).

Although the plausible beneficial effect of B cell depletion in APS is intriguing, the data on rituximab for APS criteria and non-criteria manifestations is still lacking. In the current study we describe a relatively large, real-life series of APS patients treated with rituximab in three medical centers in Israel. We also analysed the effect of this intervention on a range of APS manifestations, utilising different treatment regimens.

Patients and methods

Study population

In this retrospective study we identified 40 APS patients, diagnosed according to the revised Sapporo criteria (13), who were treated with rituximab. Patients were followed in three large medical centres in Israel during 2011–2019. This study received approval by the institutional ethics committee and fulfilled the ethical guidelines of the declaration of Helsinki (Edinburgh 2000).

Data collection

For each participant in the study, demographic information (*e.g.* age and gender), clinical data (*e.g.* clinical manifestations of APS, duration of disease, indications for Rituximab treatment, dose and regimen of rituximab, concomitant medications) and laboratory data (*e.g.* aPL antibodies, platelet counts, CRP)

were retrieved from the medical records. The clinical manifestations for which rituximab therapy was administered included: diffuse alveolar haemorrhage (DAH) defined by lung infiltrates, decrease in haemoglobin, haemoptysis and/or broncho-alveolar lavage compatible with DAH; recurrent thrombosis and/or ischaemic events while treated with anti-coagulation ± anti-aggregants; cytopenia mainly thrombocytopenia but also autoimmune haemolytic anaemia; neurological manifestations including chorea, intractable epilepsy, cognitive deterioration; renal impairments compatible with APS nephropathy (proteinuria and/or elevated creatinine with no evidence for lupus nephritis (renal biopsy was not performed d/t severe thrombocytopenia and or inability to withhold anti-coagulation therapy); cutaneous manifestations including chronic ulcers due to small vessel micro-thrombi and/or severe vasculopathy; catastrophic APS (cAPS) diagnosed according to the published criteria (14).

In this study, response to therapy was defined as: complete response (CR), if full resolution of the "indicated manifestation" was achieved and maintained for at least 12 months. No response (NR) to therapy was defined once symptoms control was not achieved despite administration of all available therapies for the specific indication and no improvement occurred after 4 months of rituximab administration. Partial response (PR) was reported once a favourable response occurred but did not meet the criteria for complete response (*e.g.* significant increase in platelet numbers although not to normal levels or partial resolution of an ischaemic events). Rituximab was administrated according to the treating physician's judgment using one of 2 regimens: (1) 2 doses of 1000 mg given twice (2 weeks apart); (2) 375mg/m^2 body surface area given once weekly for 4 doses.

Statistical analysis

Statistical analysis was performed using SPSS 24.0. For all tests $p<0.05$ was considered statistically significant. Continuous variables were described as mean ± standard deviation and categorical variables as percentages. Comparisons between groups were analysed by chi-square test or Fisher's exact test as appropriate for categorical variables, and by Student's t-test or Mann-Whitney for continuous variables.

Table I. Demographics and clinical manifestations of patients with APS treated with rituximab.

Parameter	Patients with APS (n=40)
Age (in years)	40±14
Gender (Male)	16 (40%)
Duration of APS (in years) 12.6±10	
Primary APS	31 (78%)
APS secondary to SLE	9 (22%)
*Triple positive aPLs	30 (75%)
*Double positive aPLs	10 (25%)
Indications for rituximab therapy	
Diffuse alveolar haemorrhage (DAH)	7 (18%)
#Primary APS/Secondary APS	*4/3*
Recurrent thrombosis despite adequate anticoagulation**	10 (25%)
#Primary APS/Secondary APS	*10/0*
Cytopenia (*i.e.* thrombocytopenia, AIHA)	10 (25%)
#Primary APS/Secondary APS	*7/3*
Neurological manifestations	6 (15%)
#Primary APS/Secondary APS	*6/0*
Renal involvement	2 (5%)
#Primary APS/Secondary APS	*2/0*
Skin manifestations (*e.g.* ulcers , vasculopathy)	5 (12.5%)
#Primary APS/Secondary APS	*2/3*
Catastrophic APS	2 (5%)
#Primary APS/Secondary APS	*2/0*

Data is presented as mean± standard deviation or number of patients (percentage);
*number of criteria anti-phospholipid antibodies sero-positivity.
**Warfarin or LMWH.
#Number of primary APS patients presented with the specific indication.

Results

Herein we retrospectively collected and analysed data on 40 patients with APS who were treated with rituximab during 2011-2019. This group of APS patients represents about 5.6% of the entire cohort of patients with APS followed in our centres. This cohort encompasses mostly patients with primary APS with long standing disease and 9 patients with APS secondary to SLE, all of which exhibited high titres of antiphospholipid antibodies and the majority [30 patients (75%)] were 'triple positive' (*i.e.* seropositive for all three criteria aPL: anti-cardiolipin, anti-B2GPI and lupus anticoagulant) as outlined in Table I.

Response to rituximab therapy

The response to rituximab therapy was favourable in 32 patients (80%) and in 22 patients (55%) this response was defined as complete, while 5 patients (12.5%) did not respond to this intervention and 3 patients (7.5%) died. The main indications for rituximab treatment in this cohort were recurrent thrombosis, low blood cell counts in 10 patients, 9 of whom had thrombocytopenia and one patient had refractory autoimmune haemolytic anaemia, diffuse alveolar haemorrhage, neurological manifestations in 6 patients with primary APS (*e.g.* chorea, intractable epilepsy, recurrent amaurosis fugax, and leg ulcers (Table I, Fig 1). Two treatment regimens of Rituximab were utilised in our cohort: either 2 doses of 1000mg (2 weeks apart) or a more tailored protocol of 375mg/m^2 given once weekly for 4 doses. The former regimen was given to 23 patients (58%) and the latter to 17 patients (42%). Notably, 9 patients received more than one course of therapy. Response to Rituximab differed according to the protocol. Significantly more patients achieved a complete or partial response following the tailored protocol (375mg/m^2 x4) compared to the fixed protocol (1000 mg x2) (p=0.01; Table II).

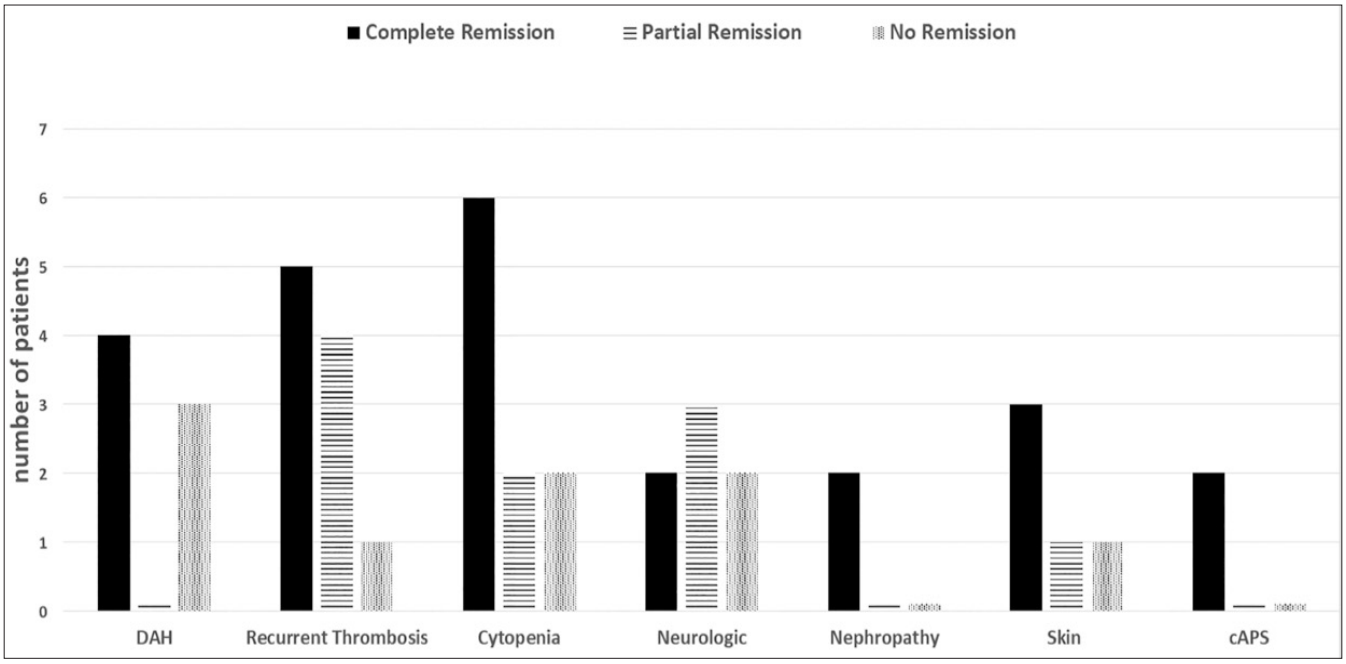

Fig. 1. Response to treatment with rituximab according to APS manifestations.
DAH: diffuse alveolar haemorrhage; cAPS: catastrophic APS.

Concomitant therapies

Concomitant therapies were prescribed to most patients in this cohort. High dose glucocorticoids (GCs) was administered in 28 patients (73%; 500–1000 mg pulses of methylprednisolone/d x3–5 in 10 patients of which 7 had pAPS, oral GCs at a dose up to 1mg/kg/d in 18 patients), hydroxychloroquine in 24 patients (60%; 17 with pAPS), cyclophosphamide in 8 patients (20%; 3 with pAPS), high dose IV immunoglobulins in 6 patients (15%; 3 with pAPS), azathioprine in 6 patients (15%; 2 with pAPS), and belimumab in 1 patient with sAPS. Additionally, 19 patients (48%) underwent plasma apheresis (3-7 exchange cycles; 15 of whom had pAPS). In this cohort 38/40 patients were treated with full dose anticoagulation, with either warfarin (target INR 2.5–3) or LMWH 1mg/kg x2/day. Two patients did not receive full dose anticoagulation due to significant thrombocytopenia, one of whom was treated with low dose LMWH (1mg/kg x1/d) and one who did not receive anticoagulation. Additionally, during the study period 1 pAPS patient who was treated with 'full dose' anti coagulants suffered from recurrent brain ischaemic events with micro-bleeding and thus anticoagulation therapy was halted. All patients with current or prior arterial events and/or recurrent thrombosis received anti-aggregants (*e.g.* aspirin 100 mg/d). in addition to anti-coagulants. Patients with intractable epilepsy received several different courses/combinations of anti-epileptic drugs.

Table II. APS response to rituximab according to treatment protocol.

Rituximab protocol:	1000mg x 2 (n=23)	375mg/m^2 x 4 (n=17)	*p*-value
All responders	**15 (65%)**	**17 (100%)**	**0.01**
Complete response	10 (43%)	12 (70%)	0.09
No response	5 (22%)	0 0.056	
Additional courses	6	3	NA
Death	3	0	NA

NA: not assessed.

Complete and/or partial response did not correlate with any of the concomitant therapies used, in comparison to patients who did not receive the particular concomitant treatment namely. For HCQ, 20/24 treated patients responded; p=0.7, for Glucocorticoids 21/28 responded; p=0.4, for IVIG 4/6 responded; p=0.5 and for Azathioprine 4/6 patients responded; p=0.5. In contrast, response to RTX inversely correlated with plasma apheresis and with cyclophosphamide treatment to which only 12/19 and 3/8 treated patients responded respectively (p=0.003 for both). Death, documented in 3 patients in this cohort, correlated with the use of cyclophosphamide as well (p=0.005).

Antiphospholipid antibody titre levels

Following rituximab treatment, aPL *titre levels* were assessed 4-6 months post therapy. In our study, aPL titres were measured prior to therapy in all patients. However, data on aPL titres prior to intervention (*i.e.* within 3 months) and in the 4–6 months following rituximab administration, using the same laboratory system were available for only 23 patients, of whom 13 experienced complete response and 10 partial or no response. A significant decrease in aPL titres was documented only in the group of patients with complete response (Table III).

Table III. Laboratory parameters following rituximab treatment.

Parameter (normal range)	Complete responders (n=13) *Pre-treatment	Complete responders (n=13) *Post-treatment	*p-value	Partial/non-responders (n=10) **Pretreatment	Partial/non-responders (n=10) **Post-treatment	**p-value
aCL IgM (0-15 U/ml)	**55 ± 49**	**9 ± 17**	**0.016**	21 ± 52	15 ± 40	0.8
aCL IgG (0-15 U/ml)	76 ± 55	45 ± 38	0.16	101 ± 70	92 ± 70	0.6
aβ2 IgM (0-15 U/ml)	**61 ± 63**	**12 ± 23**	**0.05**	23 ± 55	28 ± 70	0.9
aβ2 IgG (0-15 U/ml)	**108 ± 88**	**26 ± 33**	**0.015**	127 ± 77	109 ± 70	0.6
RVVTR (0.9-1.34)	**2.66 ± 0.94**	**1.63 ± 0.49**	**0.022**	2.26 ± 0.79	2.29 ± 1	0.95
PTTR (1.04-1.66)	**3.16 ± 1.69**	**1.57 ± 0.45**	**0.058**	2.2 ± 0.8	1.92 ± 0.7	0.9
Platelets	110 ± 100	201 ± 117	0.07	108 ± 97	175 ± 132	0.24
CRP (<5)	**79 ± 100**	**8 ± 13**	**0.053**	24 ± 32	12 ± 17	0.4

All data are presented as mean ± standard deviations. aCL: anti cardiolipin; aβ2: anti β2GPI; RVVTR: lupus anti coagulants measure by the Russel venom reagent ratio; PTTR: lupus anti-coagulant measured by PTT ratio; CRP: C-reactive protein.

Adverse events

In this cohort, serious adverse events were not reported following 54 courses of therapy. Mild hypersensitivity reactions were documented in 2 patients who were treated with anti-histamines and glucocorticoids with no need to change the protocol. One patient presented with mild neutropenia post therapy that resolved spontaneously. None of the patients in this cohort developed persistent hypogammaglobulinaemia however 5 patients remained with low immunoglobulin levels during the year of follow up, but only one developed persistently lower than usual IgM levels for a prolonged period (more than a year).

Three patients died, one with primary APS died from infections, 2 months following treatment with multiple drugs for refractory diffuse alveolar haemorrhage. Two patients with secondary APS died several months following treatment with rituximab, one of whom was treated for DAH but died due to sepsis soon after a mitral valve operation and the other from lupus cerebritis that was not compatible with PML or infection

Discussion

In this real-life observational study of 40 patients with APS, Rituximab was beneficial for the indicated manifestation in 80% of the patients, and induced a complete response in 55% of them. No serious safety alerts were reported during treatment and follow up of 54 courses of RTX as well as for the 9 patients (23%) who received several treatment courses. This is, to the best of our knowledge, the largest reported series of B cell depletion for APS, and our results stand in agreement with former reports. In a case series of 24 patients with APS(10) , 46% achieved a complete response and an additional 29% achieved a partial response. Other promising reports on the use of rituximab for APS associated recurrent thrombosis (15), thrombocytopenia (8,16), diffuse alveolar haemorrhage (17, 18), case reports of various manifestations (19) as well as recently published expert opinions (2, 7, 20) further support the notion of using the modality of B cell depletion for severe or refractory APS manifestations.

Herein, we noted a beneficial response to rituximab given in adjusted doses of 375 mg/m^2 x4 compared to a fixed dose regimen of 1000 mg x2. This comparison was rarely performed as different protocols have been used by different researchers. Interestingly, immune thrombocytopenia and cryoglobulinaemia are commonly treated with the adjusted protocol (21-24) suggesting that the management of APS manifestations may require more profound B-cell depletion, whereas rheumatoid arthritis is typically treated with the fixed dose regimen. Thus, although larger controlled studies are required for assessment of differences between regimens, one may suggest that such differences may be of importance in certain conditions and in certain populations. Particularly, most patients in this cohort received a total RTX dose of more than 2000 mg per course when using the tailored regimen.

As expected, most patients with active, difficult and even catastrophic disease, as described herein, received multiple therapies concomitantly. Estimation of the added benefit of each intervention is difficult if not impossible and therefore cannot be excluded. Nonetheless, in this study, the remission rate did not correlate with any of the other treatment modalities (*e.g.* glucocorticoids, immunosuppressive, etc.). In contrast, lack of response was linked with use of cyclophosphamide or plasma apheresis, while death was linked with the former. These associations may represent the severity of the underlining disease rather than adverse effects of the drug and require further study.

B cells role in autoimmunity was primarily based on their effector functions, as they give rise to autoantibody producing plasma cells and promote CD4$^+$ T cell responses by antigen presentation. Depletion of B cells may affect autoimmunity in many ways: elimination of autoreactive B cells and reduction of pathogenic autoantibody production occur in some patients but not in all, as rituximab has no effect on memory B cells or long-lived plasma cells. Other mechanisms by which Rituximab may downregulate autoimmunity include decreased antigen presentation to T-cells, formation of immune complexes (*e.g.* rituximab-CD20) which may act as a decoy, attracting monocytes and macrophages, leading to reduction of pathologic inflammation. Last but not least, rituximab may promote the appearance of regulatory B-cells once reconstitution

of the humoral arm of the immune system occurs (25). In this regard, APS is a classical humoral derived disease defined by the presence of autoantibodies directed at phospholipids and related proteins. Additionally, in murine models, B cell activation of CD4+ T-cells was shown to be a necessary step for the development of APS (26). However, current data regarding the mechanisms by which rituximab may modulate APS manifestations is still lacking. In this study we observed a correlation between a decrease in aPL titres and the achievement of complete remission. This stands in agreement with several reports of APS patients with recurrent thrombosis who responded well to rituximab with a significant decrease in aPL titre s measured during the first 6 months of follow up (15, 27). In another study of 24 patients with APS who were treated with rituximab, aPL titre s decreased in 4 of 5 patients who had been assessed for aPL titre s and experienced clinical improvement (10). Similarly, in APS-related thrombocytopenia complete response was linked with a decrease in aPLs (16). In contrast, in the pilot study of Rituximab for non-criteria manifestations of APS, no substantial change in the aPL profile was observed during 12 months of follow-up (12). These differences may represent different populations, different methods of aPL detection or even different timing of aPL sampling. Nonetheless, it seems that at least for some patients, a decrease in aPL titres, within a certain period of time following rituximab treatment, is associated with a favourable outcome and may possibly be used as a marker for response to therapy. Other immune modulating mechanisms, independent of autoantibody production may also be associated with a clinical response to rituximab treatment.

Our study has several limitations derived from its design as a retrospective, observational and real-life study of patients treated with multiple concomitant modalities as well as the lack of a unified serological method of assessment. Thus, the favourable outcome of treatment with the high dose RTX protocol may be biased by other therapies and particularly by multiple concomitant interventions. Our preliminary observation of a possible therapeutic regime benefit should be studies in randomised controlled studies (which this study is not). Additionally, in patients with APS secondary to SLE, certain manifestations may be attributed to both conditions and clear definition is difficult if not impossible. Still, considering the rarity of APS, the unmet need for additional therapies (even off-label) for this debilitating disease, and the lack of data, we believe that the data derived from this relatively large series may be contributory.

In conclusion, consistent with other studies and case series, we report a good safety profile and a therapeutic response to rituximab treatment for different criteria and non-criteria manifestations of APS, most particularly for severe refractory disease. In this cohort, a dose adjusted regimen resulted in a better response to Rituximab, compared to a fixed dose regimen. These differences require validation in other cohorts and may result from differences in the treatment regimens and/or due to a higher dose of the drug. Last but not least, the possible beneficial effects of rituximab may relate to different immune mechanisms of which only a decrease in aPL titres was assessed in this study and was associated with response to B-cell depletion therapy. Further prospective studies, designed to evaluate the clinical and immunological effects of B cell depletion in the management of APS manifestations, as well as the effects of combination modalities are needed to validate our results and aid in constructing evidence based guidelines for the management of this multisystem severe disease.

References

1. GARCIA D, ERKAN D: Diagnosis and management of the antiphospholipid syndrome. *New Engl J Med* 2018; 379: 1290.
2. PENGO V, DENAS G: Diagnostics and treatment of thrombotic antiphospholipid syndrome (APS): a personal perspective. *Thromb Res* 2018; 169: 35-40.
3. ARACHCHILLAGE DRJ, LAFFAN M: Pathogenesis and management of antiphospholipid syndrome. *Br J Haematol*. 2017; 178: 181-195.
4. CANAUD G, BIENAIME F, TABARIN F *et al*.: Inhibition of the mTORC pathway in the antiphospholipid syndrome. *New Engl J Med* 2014; 371: 303-12.
5. DE GROOT PG, URBANUS RT: Antiphospholipid syndrome--not a noninflammatory disease. *Semin Thromb Hemostasis* 2015; 41: 607-14.
6. SEVIM E, WILLIS R, ERKAN D: Is there a role for immunosuppression in antiphospholipid syndrome? *Hematology. Am Soc Hematol Educ Program* 2019; 2019: 426-32.
7. STOOTS SA, LIEF L, ERKAN D: Clinical insights into diffuse alveolar hemorrhage in antiphospholipid syndrome. *Curr Rheumatol Rep* 2019; 21: 56.
8. SCIASCIA S, RADIN M, CECCHI I *et al*.: Long-term effect of B-cells depletion alone as rescue therapy for severe thrombocytopenia in primary antiphospholipid syndrome. *Semin Arthritis Rheum* 2019; 48: 741-44.
9. WANG CR, LIU MF: Rituximab usage in systemic lupus erythematosus-associated antiphospholipid syndrome: A single-center experience. *Semin Arthritis Rheum* 2016; 46: 102-8.
10. PONS I, ESPINOSA G, CERVERA R: Efficacy and safety of rituximab in the treatment of primary antiphospholipid syndrome: analysis of 24 cases from the bibliography review. *Med Clin* (Barc) 2015; 144: 97-104.
11. KAEGI C, WUEST B, SCHREINER J *et al*.: Systematic review of safety and efficacy of rituximab in treating immune-mediated disorders. *Front Immunol* 2019; 10: 1990.
12. ERKAN D, VEGA J, RAMON G, KOZORA E, LOCKSHIN MD: A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. *Arthritis Rheum* 2013; 65: 464-71.
13. MIYAKIS S, LOCKSHIN MD, ATSUMI T *et al*.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295-306.
14. ORTEGA-HERNANDEZ OD, AGMON-LEVIN N, BLANK M, ASHERSON RA, SHOENFELD Y: The physiopathology of the catastrophic antiphospholipid (Asherson's) syndrome: compelling evidence. *J Autoimmun* 2009; 32: 1-6.
15. BAKSHI J, STEVENS R: Rituximab therapy for recurrent thromboembolic disease in antiphospholipid syndrome. *Lupus* 2013; 22: 865-67.
16. GAMOUDI D, CUTAJAR M, GAMOUDI N *et al*.: Achieving a satisfactory clinical and biochemical response in antiphospholipid syndrome and severe thrombocytopenia with rituximab: two case reports. *Clin Case Rep* 2017; 5: 845-48.
17. AAKJAER S, BENDSTRUP E, IVARSEN P, MADSEN LB: Continous Rituximab treatment for recurrent diffuse alveolar hemorrhage in a patient with systemic lupus erythematosus and antiphosholipid syndrome. *Respir Med Case Rep* 2017; 22: 263-65.
18. SCHEIMAN ELAZARY A, KLAHR PP, HERSHKO AY, DRANITZKI Z, RUBINOW A, NAPARSTEK Y: Rituximab induces resolution of recurrent diffuse alveolar hemorrhage in a patient with primary antiphospholipid antibody syndrome. *Lupus* 2012; 21: 438-40.
19. KUMAR D, ROUBEY RA: Use of rituximab in the antiphospholipid syndrome. *Curr Rheumatol Rep* 2010; 12: 40-44.

20. DOBROWOLSKI C, ERKAN D: Treatment of antiphospholipid syndrome beyond anticoagulation. *Clin Immunol* 2019; 206: 53-62.
21. NEUNERT C, TERRELL DR, ARNOLD DM *et al*.: American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv* 2019; 3: 3829-66.
22. NEUNERT CE: Management of newly diagnosed immune thrombocytopenia: can we change outcomes? *Blood Adv* 2017; 1: 2295-301.
23. OSTOJIC P, JEREMIC IR: Managing refractory cryoglobulinemic vasculitis: challenges and solutions. *J Inflamm Res* 2017;10: 49-54.
24. ROCCATELLO D, SCIASCIA S, BALDOVINO S *et al*.: Improved (4 plus 2) rituximab protocol for severe cases of mixed cryoglobulinemia: a 6-year observational study. *Am J Nephrol* 2016; 43: 251-60.
25. MUSETTE P, BOUAZIZ JD: B cell modulation strategies in autoimmune diseases: new concepts. *Front Immunol* 2018; 9: 622.
26. KHATTRI S, ZANDMAN-GODDARD G, PEEVA E: B-cell directed therapies in antiphospholipid antibody syndrome--new directions based on murine and human data. *Autoimmun Rev* 2012; 11: 717-22.
27. GKOGKOLOU P, EHRCHEN J, GOERGE T: Severe antiphospholipid antibody syndrome - response to plasmapheresis and rituximab. *J Dermatolog Treatment* 2017; 28: 564-66.