Antiphospholipid syndrome (APS) is an autoimmune disorder that has been classically characterised by the presence of thrombotic episodes and/or obstetric morbidity along with the maintained existence of antiphospholipid antibodies (APAs)\(^1\). Patients who experience this clinical-analytical spectrum fulfil Sydney’s 2006 classification criteria for APS\(^2\). However, it should not be forgotten that there is a wide spectrum of clinical manifestations that, without being included in the classification criteria (livedo reticularis, thrombocytopenia, haemolytic anaemia, valvulopathy, nephropathy associated to APA, skin ulcers or cognitive dysfunction), can be symptomatic of APS\(^3\). Finally, there is an entity known as catastrophic APS, defined by the presence of thrombosis in multiple locations in a short period of time, with the subsequent development of multiple organ failure\(^4\).

Based on its prothrombotic nature, the standard treatment for APS is marked by the administration of anticoagulants (vitamin K antagonists or low molecular weight heparin) and/or antiaggregation\(^5\). Other treatments that can contribute with an additional effect are hydroxychloroquine, the use of which in patients with systemic lupus erythematosus (SLE) with APA has been associated with a decrease in the thrombosis rate\(^2\), and statins, based on their anti-inflammatory, immunomodulatory and antithrombotic properties\(^6\).

However, based on the key role of APAs, and by extension, B lymphocytes in this entity, there is increasing interest in observing the effects that the treatments targeted against them can have on APS\(^7\). Animal models have been developed to study the effect of modulatory treatments on the antibodies producing cells, specifically, through an inhibition of co-stimulation with CTLA4-Ig and through BAFF antagonists, with positive effects in both cases\(^8,9\).

The available data on the use of this type of treatment in humans is basically restricted to rituximab (RTX), a chimeric monoclonal antibody used against the antigen CD20 of B cells, the use of which is approved for B cell lymphoma, rheumatoid arthritis, granulomatosis with polyangiitis and micropolyangiitis. Two clinical trials on the use of RTX in SLE (EXPLORER and LUNAR) did not show superiority over the baseline treatment, but their results are questionable due to the high doses of glucocorticosteroids used to treat the patients in the “placebo” group\(^10,11\). In fact, it is still currently used in severe or refractory cases, although the indication is not included on the technical data sheet.

In relation to APS, its possible efficacy was initially shown in clinical cases, case series and registries of patients with catastrophic APS, such as the CAPS Registry\(^12–15\). In most cases, it was administered as a treatment for clinical manifestations that are not included in Sydney’s criteria, such as thrombocytopenia or autoimmune haemolytic anaemia. It is worth mentioning that in almost all the published cases, RTX was not used in isolation but, rather, concomitantly with glucocorticosteroids and other immunosuppressants, clearly limiting any assessment of its efficacy. Concurrently, some authors have demonstrated a maintained decrease in APA levels after treatment with RTX\(^12–14\) but this has not been confirmed in other cases\(^16\).

If we consider the data published in the CAPS Registry\(^15\), in a total of 20 patients treated with RTX, we observe that 40% received this as first line treatment, while it was used as a second therapeutic step in the remaining 60%. Mortality was 20% (4 patients, including 2 initially treated with RTX). Of the remaining 16 patients, 12 achieved complete remission and 2 required further RTX administration due to skin necrosis and recurrent thrombocytopenia, respectively. The scarce number of patients makes it difficult to assess the findings obtained, although they could guide us towards a potential role for RTX in patients with catastrophic APS.

In 2013, Erkan et al. published a prospective pilot study on the administration of RTX in 19 patients with primary APS with clinical manifestations outside Sydney’s\(^16\) criteria, in particular valvulopathy, thrombocytopenia, cognitive dysfunction and skin ulcers. This study confirmed an acceptable safety profile for the drug in this
group of patients (with 26% of pro-infusional reactions, none of which required hospitalisation, and a severe infection rate of 16.9 per 100 patients/year) without confirming the diminishing effects on the levels of APA that have been observed by other authors in isolated cases. In terms of efficacy, except in the case of skin ulcers (which showed greater uniformity in terms of good results), the response was somewhat irregular regarding the remaining clinical manifestations but, once again, the scarce number of patients included limits this data [10].

The study in question, published in this edition of Medicina Clínica [17], includes a review of the articles published up to 2013 in which cases of patients with primary APS treated with RTX are analysed, excluding those with catastrophic APS. The main indications for RTX treatment were thrombocytopenia and skin involvement, followed by neurological and valvular involvement, autoimmune haemolytic anaemia and alveolar haemorrhage. Thus, the patients enrolled have manifestations that are mostly not included in Sydney's criteria. However, it is interesting that the treatment indications in 2 of the 24 patients were thrombotic manifestations: one patient with cerebral venous thrombosis concomitantly with thrombocytopenia, and another with recurrent transient ischaemic attack (TIA) despite the administration of anti-coagulant and antiaggregant treatment. It is worth mentioning that among those cases where RTX was used as the primary line of treatment (a total of 7: one cerebral venous thrombosis, one with symptoms of recurrent TIA, 2 cases of valvulopathy, 2 cases of skin involvement and one case of cognitive dysfunction), 5 achieved complete remission, among them, the 2 patients with thrombotic symptoms. However, except in the case of cerebral venous thrombosis, in which RTX (along with glucocorticosteroids iv and acetazolamide) was the only treatment administered, for the rest of the patients it was administered simultaneously with anticoagulation and/or antiaggregation treatments, and in some cases, hydroxycloroquine.

Overall, the response varied and slightly more than half of the patients achieved the complete clinical response as defined according to the specific criteria of the different authors. There was a lack of response in 16.6% of patients and the rest showed partial improvement. In terms of specific manifestations, it is surprising that the 8 patients with skin manifestations, ulcers and livedoid vasculopathy, which are in general very difficult to manage, responded to the treatment completely (62.5%) or partially (27.5%). A high frequency of complete response was also observed in patients with thrombosis (100%) and valvulopathy (66.7%), even if in this instance the number of cases was lower (2 and 3, respectively). The effects were more irregular in patients with other manifestations, such as thrombocytopenia, haemolytic anaemia and haemorrhagic deterioration.

On the other hand, this review confirms the good safety profile of the drug. It should be noted that RTX efficacy is not invariably associated with a decrease in or elimination of APAs, as in different situations the cases of complete or partial remission do not show significant modifications in their levels. However, only 9 patients had sufficient data to analyse the evolution of APA titres after treatment, so the significance of this observation is also limited.

What is the practical value of the review by Pons et al.? Overall, we consider it highly premature to infer a potential use of RTX as the first therapeutic option for patients with APS. Our caution is based on the scarce number and heterogeneity of patients, the difficulty in accessing part of the clinical information for many of them, the additional effect of the other drugs administered and, particularly, the difficulty in establishing objective response criteria, in particular, in the cases of cardiac valvular condition and thrombosis. However, the results of this study invite us to consider the early administration of RTX in patients

with severe dermatological manifestations of APS, in particular ulcers and skin necrosis, which are generally chronic and very difficult to manage at a therapeutic level with the customary means.

At the opposite end of the scale we find thrombotic manifestations, for which there is a generally efficient therapeutic option [7]. In cases when progress is deficient, instead of the standard anti-coagulant treatment, it seems more reasonable to use more conventional drugs such as hydroxychloroquine or statins and, particularly, to insist on maintaining adequate control of vascular risk factors. In other cases with APS manifestations not included in Sydney's classification criteria, RTX can be considered an option when an added immunosuppressant treatment is required and the clinical manifestations are resistant to that treatment.

Finally, we have yet to determine the attitude we should adopt in the case of patients who, as a result of RTX treatment, continue to neutralise APAs. Even if the possibility of discontinuing the anti-coagulant treatment is included in the cases in which antibodies spontaneously disappear [8], this decision should always be personalised, taking into consideration together with the patient the risks and consequences of re-thrombosis in the face of the possibility of haemorrhage and the discomfort of chronic anti-coagulant treatment.

References

