BAFF blockade restores refractory thrombocytopenia of primary antiphospholipid syndrome: a case series

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The clinical efficacy of belimumab, a BAFF-targeting monoclonal antibody, has long been determined in SLE-related thrombocytopenia; however, its role in thrombocytopenia associated with primary antiphospholipid syndrome (APS) remains unknown. Given the role of B-cell dysregulation in APS (1), and the link between thrombocytopenia and increased thrombotic risk in these patients (2) the presented case series aims to provide an exploratory assessment of the efficacy and safety of belimumab, as an add-on therapy for refractory primary APS-related thrombocytopenia.

All patients satisfied the 2023 ACR/EULAR classification criteria for APS (3) but not for any other autoimmune disease (online Supplementary file). Patients' characteristics, disease course and management until belimumab administration are detailed in Table I. The study was approved by the Ethics Committee of the Medical School, National and Kapodistrian University of Athens, Greece (protocol no: 750/25.5.2023). Data were collected and analysed after all patients' written informed consent, whereas the general data protection regulations and the Helsinki Declaration were routinely followed.

Patient 1, prior to APS diagnosis, was monitored for three years for recurrent severe thrombocytopenia (<10x10^9/L), refractory to conventional and second-line therapies, *i.e.* glucocorticosteroids, eltrombopag, intravenous-immunoglobulin, cyclophosphamide, cyclosporine, azathioprine, and splenectomy. Following diagnosis, she continued to experience thrombocytopenia flares (<50×10^9/L) despite therapy (Table I), resulting in repeated hospitalisations owing to disease activity and treatment-related complications, including infections and a metatarsal osteoporotic fracture.

Patient 2 displayed recurrent episodes of moderate thrombocytopenia (50–70x10^9/L), despite immunosuppression for several years (Table I). The addition of rituximab stabilised but did not normalise platelet counts (~95×10^9/L). Frequent infections, imposed repeatedly oral antibiotics and occasional hospitalisation for intravenous therapy.

Patient 3 achieved stabilisation of platelets (80–100×10^9/L) following immunosuppressive treatment, however remained dependent on low-dose corticosteroids for persistent mild thrombocytopenia (Table I).

All patients initiated intravenous belimumab 10 mg/kg/month, administered as add-on therapy with mycophenolate mofetil-MMF/methylprednisolone (Patient 1), azathioprine (Patient 2), and azathioprine/meth 1 and Patient 2). All regained (after 3–6 months) and sustained normal platelet counts over the 24-month follow-up period (Supplementary Fig. S1); methylprednisolone was discontinued in Patient 1 and Patient 3 (after 10 and 6 months, respectively), while the MMF dose in Patient-1 was reduced to 1 g qd. Belimumab was well tolerated with no adverse effects. Moreover, no new thrombotic events occurred; two of the three patients became negative for LAC and maintained stable anticoagulation on a reduced acenocoumarol dose. Although all patients displayed antinuclear antibody reactivity at some point during follow-up, none ever showed clinical manifestations consistent with SLE or other autoimmune disease (Suppl. Table S1).

Besides non-immune mechanisms (4), APS-associated thrombocytopenia may owe to anti-platelet autoantibodies (5). In this context, the rationale for B-cell-depleting therapy in APS-associated thrombocytopenia is the elimination of pathogenic autoantibody-producing B-cells. Although B-cell-depletion by rituximab has been shown to diminish pathogenic antibodies in SLE, its efficacy in suppressing aPL production, remains unclear (6).

Belimumab has shown efficacy in SLE-associated thrombocytopenia, in patients with or without aPL, and in modulating aPL levels (7). Although, it has been reported to improve thrombocytopenia in an APS-case (8), its efficacy in primary APS-related thrombocytopenia remains unknown. Sporadic APS-cases with recalcitrant microthrombotic complications have been shown to benefit from belimumab administration (9), while there is evidence that belimumab reduces aPL titres in APS (10).

Herein, we provide first evidence that belimumab may hold promise as add-on therapy in refractory primary APS-related thrombocytopenia, thus warranting prospective evaluation to establish its therapeutic role. However, the small sample size and absence of a control group restrict causal inference and generalisability. While

Table I. Clinical features and disease course of the three APS patients up to belimumab initiation.

Patient 1 Female 25 years old Follow-up period: 2014-2025	**2023 ACR/EULAR criteria fulfilled at APS diagnosis:** Thrombosis of the transverse sinus and left subclavian and jugular vein, thrombocytopenia (25x10^9/L), persistently positive LAC (**total score: 10**) **APS-related treatment** **At diagnosis:** PRDL 1 mg/kg, IVIG 2 gr/kg, low molecular weight heparin (administered when PLTs >50x10^9/L). **Maintenance:** MMF 3 gr qd, MLP 32 mg qd with gradual tapering, acenocoumarol (target INR: 3-4), acetylsalicylic acid 80 mg qd, calcium and vitamin D supplementation. **Subsequent APS course** Thrombocytopenia recurred during tapering of MLP to 16 mg daily, prompting the addition of iv RTX at a dose of 2 gr every 6 months. **2020-2023:** While on MMF/RTX/MLP, occurrence of 3 thrombocytopenia flares (20-50x10^9/L) upon MLP tapering to 6 mg qd. **2023:** Metatarsal osteoporotic fracture, despite risendronate sodium (35 mg/week) treatment. **2023:** Initiation of belimumab*
Patient 2 Male 37 years old Follow-up period: 1999-2025	**2023 ACR/EULAR criteria fulfilled at APS diagnosis:** Recurrent DVT of the lower extremities, pulmonary emboli episode, thrombocytopenia (50x10^9/L), persistently positive LAC, moderately positive IgG anti-CL (**total score: 14**) **APS-related treatment** **At diagnosis:** PRDL 1mg/kgr with gradual tapering-off, monthly iv pulses of CYC (total cumulative dose: 6 gr), low molecular weight heparin (administered when PLTs >50x10^9 /L), calcium and vitamin D supplementation. **Maintenance:** AZA 175 mg qd, acenocoumarol (target INR: 3-4). **Subsequent APS course** Recurrent episodes of thrombocytopenia (50-70x10^9/L). **2021:** Addition of iv RTX (2 gr every 6 months), while on AZA (175 mg qd). **2021-2023:** stable but subnormal platelet counts (95x10^9/L). **2023:** initiation of belimumab*
Patient 3 Male 45 years old Follow-up period: 2018-2025	**2023 ACR/EULAR criteria fulfilled at APS diagnosis:** Pulmonary emboli and adrenal haemorrhage, thrombocytopenia (47x10^9/L), highly positive IgG anti-CL and highly positive IgG anti-β2GPI (**total score: 17**) **APS-related treatment** **At diagnosis:** PRDL 1 mg/kg, gradual tapering to MLP 4 mg qd, monthly iv pulses of CYC (total cumulative dose: 6 gr), low molecular weight heparin (administered when PLTs >50x10^9 /L), calcium and vitamin D supplementation. **Maintenance:** AZA 150 mg qd, MLP 4 mg qd, acenocoumarol (target INR: 3-4), acetylsalicylic acid 80 mg qd. **Subsequent APS course** **2019-2023:** PLT counts stabilised at approximately 80–100x10^9/L; however, further steroid tapering was constrained by persistent mild thrombocytopenia (80-100x10^9/L). **2023:** initiation of belimumab*

DVT: deep vein thrombosis; anti-CL: anti-cardiolipin antibodies; anti-β2GPI: anti-β2GPI antibodies; LAC: lupus anticoagulant; PRDL: prednisolone; GPI: glycosylphosphatidylinositol; MLP: methylprednisolone; iv: intravenous, IVIG: intravenous immunoglobulin; PLT: platelets; MMF: mycophenolate mofetil; RTX: rituximab; CYC: cyclophosphamide; AZA: azathioprine; INR: International normalised ratio test**.** * see main text.

these initial clinical observations should be approached with caution, they do provide valuable insights for designing future large-scale, controlled trials.

O.D. Argyropoulou[1], *MD, PhD*
C. Tsironis[1], *MD*
I. Stergiou[1], *MD, PhD*
P.G. Vlachoyiannopoulos[1,2], *MD, PhD*
M.N. Manoussakis[1,2], *MD, PhD*

[1]Department of Pathophysiology,
[2]Joint Program for Rheumatology, Medical School, National and Kapodistrian University of Athens, Greece.

Please address correspondence to:
Ourania D. Argyropoulou
Academic Instructor of Pathophysiology - Rheumatology,
Department of Pathophysiology,
School of Medicine, National & Kapodistrian University of Athens,
75 Mikras Asias Str.,
11527 Athens, Greece.
E-mail: oargyrop@med.uoa.gr

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