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Anticardiolipin and anti-Beta 2 glycoprotein-I antibodies disappearance in patients with Systemic Lupus Erythematosus and Antiphospholipid Syndrome while on belimumab

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Running Title: aPLnegativization in SLE and APS patients treated with belimumab

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Sir,

The current management of Antiphospholipid Syndrome (APS) centres on attenuating the pro-coagulant state while balancing the haemorrhagic risks[1]. This approach relies mainly on a thrombo-prophylaxis strategy rather than targeting pathogenic antiphospholipid antibodies (aPL)-mediated pathways.

Herewith, we report the aPL disappearance in three patients with APS associated to Systemic Lupus Erythematosus (SLE) while on treatment with belimumab, potentially paving the way for development of new targeted therapies for APS. Belimumab is a monoclonal antibody that works by blocking the B-lymphocyte stimulator and avoiding B-cell activation[2]. It is the first biological drug approved for the treatment of autoantibody positive SLE in active phase, and it has shown its capability to reduce the antibodies levels, including anti-double stranded-DNA[3]. Intriguingly, in murine models of APS in the setting of SLE, Belimumab proved its ability to stop disease progression and to reduce mortality rate [4]. However, its use in APS patients needs further investigation.

After chart-reviewing all the aPL-positive SLE patients treated in our centre with belimumab, investigating the changes in the aPL profile, we identified three patients with diagnosis of SLE[5] and APS (fulfilling Sydney classification criteria)[6] and persistent aPL positivity (confirmed in more than 6 occasions over the previous 5 years before starting Belimumab) in whom we observed aPL disappearance. Clinical characteristics are detailed in Table 1 and aPL testing methodology is detailed in Supplementary Material S1. All patients received belimumab for active SLE (i.v. 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter). After 8 months since belimumab was started, *Patient#1* became persistently negative for anti- β 2-glycoprotein I antibodies (anti- β 2GPI), while anti-cardiolipin

antibodies (aCL) titre significantly decreased. While on treatment, anti- β 2GPI and aCL levels both turned negative in *Patient#2*. Interestingly, after being on belimumab for one year, she planned a pregnancy and preferred to suspend the treatment, after 8 months since suspension, anti β 2GPI antibodies were detectable again. *Patient#3* was persistently negative for aCL while being on belimumab(28 months). When he discontinued the therapy for lack of response, aCL antibodies returned positive after 2 months. Figure 1 illustrates aPL titres of the three patients in relationship with belimumab therapy. Two patients (#1 and #3) persistently tested positive for LA despite Belimumab treatment. No patients experienced hypogammaglobulinemia while on belimumab and IgG/IgM levels were constantly within normal range. Of note, none of the patients was started on a concomitant immunosuppressive treatment when Belimumab was begun. However, a synergic role of hydroxychloroquine in the aCL and anti-beta2GPI disappearance cannot be excluded.

Persistent aPL disappearance is a hot topic of discussion in the field of APS, but the clinical significance of sero-negativization is still to be elucidated[7,8]. At the best of our knowledge, despite its limitations (e.g. sample size and retrospective design), this pilot study is the first report of aPL negativization after starting therapy with belimumab. Even more interesting, after stopping the treatment (mean time of two months) patients turned to be positive tested for IgG aPL again. The clinical relevance of these findings should be investigated in prospective multicenter studies, but if confirmed, they might modify the therapeutic management of APS patients. Potentially, the current 'anti-thrombotic' approach to APS patients will be at least combined in the future with an 'immunomodulatory' approach.

References

- 1 Khamashta MA, Cuadrado MJ, Mujic F, *et al.* The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995;**332**:993–7.
doi:10.1056/NEJM199504133321504
- 2 Baker KP, Edwards BM, Main SH, *et al.* Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum* 2003;**48**:3253–65. doi:10.1002/art.11299
- 3 Radin M, Cecchi I, Schreiber K, *et al.* Immunotherapies in phase II and III trials for the treatment of systemic lupus erythematosus. *Expert Opin Orphan Drugs* 2017;**5**.
doi:10.1080/21678707.2017.1257937
- 4 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. doi:10.1016/j.autrev.2011.12.011
- 5 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;**40**:1725.
doi:10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y
- 6 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. doi:10.1111/j.1538-7836.2006.01753.x
- 7 Sciascia S, Coloma-Bazán E, Radin M, *et al.* Can we withdraw anticoagulation in patients with antiphospholipid syndrome after seroconversion? *Autoimmun Rev* Published Online First: 2017. doi:10.1016/j.autrev.2017.09.004
- 8 Radin M, Cecchi I, Pérez-Sánchez C. Antiphospholipid antibodies negativization: Time for testing for non-criteria aPL? *Lupus* 2017;**26**. doi:10.1177/0961203317711014

Legend of tables and Figures

Table 1. *Characteristics of the patients included in the study*

Figure 1. *aPL titers of the three patients in relationship with belimumab therapy*

Table 1. Characteristics of the patients included in the study

	Sex	Age	Diagnosis	Associated Autoimmune Disease	aPLpositivity	APS ClinicalEvents	Indication for starting belimumab	Concomitant immunomodulant treatment	Previous Immunomodulant treatment
Patient #1	M	51	APS	SLE	LA, aCLIgG, anti-β2GPI IgG	Sub-poplitealarterialthrombosis	Cutaneous*(face, upper trunk, arms) and articular involvement**	Low doses of steroids (5 mg/dl) and HCQ	IVIg, high doses of steroids
Patient #2	F	33	APS	SLE	aCL IgG, anti-β2GPI IgM	3 miscarriages <10 th week of gestation	Haematological *** and articular involvement**	Low doses of steroids (5 mg/dl) and HCQ	MMP, high doses of steroids, IVIg, AZA
Patient #3	M	39	APS	SLE	LA, aCLIgG	3 episodes of DVT, severe thrombocytopenia	Haematological **** involvement	Low doses of steroids (5 mg/dl)	High doses of steroids, RTX and CYC

APS –Antiphospholipid Syndrome; SLE – Systemic Lupus Erythematosus; aPL – antiphospholipid antibodies; LA- Lupus Anticoagulant; aCL- anticardiolipin antibodies; β2GPI- anti-β2Glycoprotein I antibodies; DVT – Deep Vein Thrombosis; HCQ – hydroxychloroquine;IVIg, intravenous immunoglobulin; AZA, azathioprine; Rituximab, RTX; MMP, Mycophenolate; CYC, Cyclophosphamide, CYC.

*Defined as Annular scaly plaques, hypopigmentation; scaly erythematous patches, reticulate erythema

**Defined as inflammatory arthritis involving more than 3 joints

***Defined as thrombocytopenia (<100.000 platelets $\times 10^9/L$), leucopenia(<2.500 white blood cells $\times 10^9/L$) and anemia (Hemoglobin <9g/dL)

**** Defined as thrombocytopenia (<50.000 platelets $\times 10^9/L$), and leucopenia(<3.000 white blood cells $\times 10^9/L$)

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Authors Contribution

ER and SS designed the study, performed data analysis and drafted the manuscript. ER, IC, DR1, MR,DR2, and SS gave a substantial contribution to concept and study design and participated in the interpretation of data. All the Authors gave the final approval of the version to be published.