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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/94497> since

Published version:

DOI:10.1177/0961203311400115

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UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Lupus an International Journal, vol. 20, 2011

DOI:10.1177/0961203311400115

S Sciascia, C Naretto, D Rossi, M Bazzan and D Roccatello, Sage Journal , 2011
vol. 20 no. 10, pp. 1106-1108

The definitive version is available at:

<http://lup.sagepub.com/>

Title page

**Treatment-induced downregulation of antiphospholipid antibodies: effect of rituximab alone
on clinical and laboratory features of antiphospholipid syndrome**

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Sir,

in 2000, a 20-year-old woman came to our attention with aphasia, transitory dysarthria, (CT-scan compatible with stroke) and thrombocytopenia (platelet-count $29 \times 10^9/l$). Laboratory tests revealed: anticardiolipin antibodies (aCL, ELISA kit Phadia, Uppsala, Sweden, EliA Cardiolipin IgG/IgM, normal value <40 U/L) $328/15$ U/L, anti-beta-2GlycoproteinI antibodies (ELISA kit Phadia, Uppsala, Sweden, EliA $\beta 2$ Gliocprotein I IgG/IgM, normal value < 40 U/L) $104/9$ U/L, and positivity for Lupus Anticoagulant (LAC). LAC measurement included: dilute Russell's viper venom time (dRVVT, Hemosil, LA-screen/confirm, Instrumentation Laboratory, Lexington,USA), partial thromboplastin time-LA (PTT-LA, Diagnostica Stago, Asnieres,France), silica clotting time (SCT, HemosIL™, DiaPharma Group, Inc.Ohio, USA), kaoline clotting time (KCT, homemade, according to Exner) (1). If PTT-LA was prolonged, the hexagonal phospholipid neutralization test was performed as confirm (STACLOT-LA, Diagnostica STAGO, Asnières, France). Thus, a diagnosis of Primary Antiphospholipid Syndrome (PAPS) was made once antiphospholipid antibody (aPL) positivity was confirmed 3 months later (2). Therapy with prednisone (50mg/day) and intravenous immunoglobulins (IVIG, 400mg/kg/d for 5 days) was started resulting in an increase in platelet count. Oral anticoagulation therapy (OAT) was started when the platelet-count reached $60 \times 10^9/l$. Platelet levels increases up to $110 \times 10^9/l$ within 4 weeks and remained stable between 130 and $140 \times 10^9/l$ for 4 months, when dropped again to $70 \times 10^9/l$. Then the patient was treated with adjusted doses of prednisone (37,5mg/day) and IVIG (400mg/kg/d for 5 more days). Prednisone treatment was slowly tapered to a daily dose of 7.5mg and finally discontinued in May 2007, when platelet counts were between 120 and $150 \times 10^9/l$.

In 2009, she presented with a worsening of thrombocytopenia (platelet count $40 \times 10^9/l$) and she was treated with the same scheme of IVIG, with partial response (platelet count up to $90 \times 10^9/l$). She relapsed within 3 weeks. Splenectomy was not performed due to the high risk of thromboembolic and/or haemorrhagic complications.

After ruling out possible contraindications, treatment with Rituximab (RTX) was started at the conventional weekly-dose of 375 mg/m² (days 1, 8, 15 and 22). Two more monthly doses later than the last infusion (day 22) were administered, based on the protocol we employ for mixed cryoglobulinemia with good results on long-lasting disease remission (3). Prednisone treatment (daily dose of 10 mg at day 1) was tapered and finally discontinued 4 weeks after first RTX-infusion. No other immunosuppressive drugs were associated. Treatment was well tolerated and no side effects were observed.

RTX administration led to an increase in the platelet count (Fig.1). In addition, aCL, anti Beta2-GPI antibodies and LAC ratio were down-regulated (Fig.1).

In this case, RTX-induced down-regulation of aPL was observed, and it was associated with a significant improvement in thrombocytopenia, thus allowing OAT to be administered.

Successful amelioration of thrombocytopenia in APS after treatment with immunosuppressive therapy has previously been reported (4). However, a non negligible percentage of patients becomes resistant/nonresponsive to immunosuppression, and sometimes splenectomy cannot be performed because of the high risk of bleeding and/or thrombotic events. Some authors have reported that RTX is effective in treating APS and reducing aPL(5) but drug-induced aPL downregulation remains a challenge (6). Notably, in a observational study in patients with Systemic Lupus Erythematosus RTX resulted in a significant reduction in levels of IgG aCL (7)

To our knowledge, this is the first report showing downregulation of aPL after RTX alone in a PAPS patient who was not treated with immunosuppressive drugs prior to anti-CD20 antibody therapy. Some Authors reported a close correlation between aCL titre reduction and an improvement in platelet count in patients with primary APS who were treated with RTX for thrombocytopenia. However, these findings were observed in refractory cases following previous immunosuppressive drug administration in addition to RTX (8, 9, 10).

Of note a 4 plus 2 protocol of Rituximab administration was employed (3). In our experience of treatment of idiopathic and secondary microscopic vasculitis, this scheme obtained more prolonged

remissions, especially in mixed cryoglobulinemia where time to relapse was found delayed up to 54 months.

Moreover, it has been hypothesised that B-cells are involved in the aPL-induced clinical manifestations of the disease (6) and it would be reasonable to assume that RTX alone (with no other immunosuppressant drug) may be useful in the management of APS. To date, after a 10-month follow-up period, the patient is well and her platelet count is within the normal range. OAT is ongoing.

Despite the limits related to the relatively short follow-up, this report may represent a starting point for further studies that could provide us with a better understanding of the mechanisms involved in the pathogenesis of aPL production.

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Figure 1 Legend

RTX administration led to an increase in the platelet count (Panel A). In addition, aCL, anti Beta2-GPI antibodies (Panel A) and LAC ratio were down-regulated. (Panel B). LAC ratio: LAC screen (1:1)/LAC confirm (1:1). LAC measurement included: dilute Russell's viper venom time (dRVVT, Hemosil, LA-screen/confirm, Instrumentation Laboratory, Lexington,USA), partial thromboplastin time-LA (PTT-LA, Diagnostica Stago, Asnieres,France), silica clotting time (SCT, HemosIL™, DiaPharma Group, Inc. Ohio, USA), kaoline clotting time (KCT, homemade, according to Exner)[3]. If PTT-LA was prolonged, the hexagonal phospholipid neutralization test was performed as confirm (STACLOT-LA, Diagnostica STAGO, Asnières,France).

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.