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Long-Term Effect of B-cells depletion alone as rescue therapy for severe thrombocytopenia in Primary Antiphospholipid Syndrome

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Short Title

Rituximab for severe thrombocytopenia in PAPS

Key words:

Antiphospholipid syndrome; APS; primary APS; antiphospholipid antibodies; aPL; extra-criteria; thrombocytopenia; Thrombosis; Autoimmunity

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Abstract

Objectives: To investigate the long term effect of B-cell depletion therapy with Rituximab (RTX) alone as rescue therapy in primary antiphospholipid syndrome (PAPS) patients with severe thrombocytopenia.

Methods: We retrospectively retrieved data from patients met the following inclusion criteria: a) persistent aPL positivity and fulfilled the Sydney criteria for PAPS b)presented with severe thrombocytopenia (platelets <50.000/mm^3) c) were treated with RTX as a rescue therapy d) had at least 1 year of follow-up after B-cells depletion therapy.

Results: This retrospective study included 6 consecutive female PAPS patients [median age 49.5 (range 38-66)] who presented with severe thrombocytopenia (platelets < 50.000/mm^3, mean value 31.000±9.000/mm^3). We observed a full response (defined as >150.000 platelets/mm^3) after treatment with RTX in 5 out of 6 patients (83.3%). Among responders, after a median follow-up of more than 4 years, we observed a median time free from relapse of 43 months (range 12-97). One patient did not respond to the B-cell depletion therapy and was treated with a splenectomy one month after RTX therapy and platelets levels normalized after 3 months. No adverse events were reported, no patients developed significant infections. Importantly, the patients required no further maintenance therapy for the thrombocytopenia.

Conclusion: In one of the longest-term observation (median 43 months) studies, sustained clinical remission of severe thrombocytopenia without immunosuppressive maintenance therapy was obtained by RTX alone in patients with PAPS and severe thrombocytopenia intolerant or refractory to conventional therapy.

Significance and Innovations

1- The use of immunosuppressive drugs in APS is limited to very selected cases

2- Long-term data on the efficacy of rituximab alone for severe thrombocytopenia in PAPS are missing

3- This long-term retrospective study included 6 consecutive PAPS patients who presented with severe thrombocytopenia

4- Sustained clinical remission was obtained by RTX alone in PAPS patients and severe thrombocytopenia

1. Introduction

Therapy and management of systemic autoimmune diseases such as systemic lupus erythematosus and systemic vasculitis has been recently revolutionized by the use of novel immunosuppressive agents that drastically changed the course of these diseases [1,2].

While immunosuppressive drugs may be helpful in patients with active systemic autoimmune diseases, their use in antiphospholipid syndrome (APS), and particularly in primary APS (PAPS), is still controversial, and limited to very selected cases of catastrophic APS or in severe cases refractory to standard therapy [3,4]. The presence of thrombocytopenia is considered to be of critical importance in patients with antiphospholipid antibodies (aPL)[5,6] and represents one of the few indications for immunosuppression in the management of APS. aPL-related thrombocytopenia is often mild to moderate, and is usually associated with a minimal risk of bleeding[7]. However, severe thrombocytopenia occasionally occurs in patients with APS, and its management is challenging, mainly due to the concomitant anticoagulation therapy.

B-cells are likely to play a central role in the generation of the aPL-induced clinical manifestations of the disease, so they might constitute a logical therapeutic target in APS.

Rituximab (RTX) is a chimeric monoclonal antibody against CD20 receptor, selectively binds CD20 positive cells, which ultimately results in B cell depletion for at least 6–9 months in over 80% of patients [8]. In recent studies, the use of RTX has been reported to be effective in controlling some but not all extra-criteria manifestations of APS[3], however, due to the low prevalence of APS and its non-criteria manifestations, data on the use of B cell depletion therapy is still lacking.

In this study, we aimed to investigate the long term efficacy of RTX rescue therapy alone in the management of severe thrombocytopenia in patients with PAPS.

2.1 Patients and Methods

2.2 Patients

We retrospective chart reviewed all APS patients who attended the S. Giovanni Bosco Hospital, Turin, Italy during the last 10 years. Inclusion criteria to the study included:

a) persistent aPL positivity and fulfilled the Sydney criteria for primary PAPS, with no underlying connective tissue disease [9].

b)treatment with RTX as a rescue therapy (e.g. because they were refractory/intolerant/contraindicated to standard therapy) for the management of severe thrombocytopenia (defined as platelets <50.000/mm^3), confirmed with at least two examinations with a complete blood count and evaluation of the peripheral blood smear[10].

c) minimum of at least one year of follow-up after B-cells depletion therapy.

RTX was administered at the dose of 375 mg/m^2 on days 1, 8, 15, 22.

2.4 Autoantibody detection

The aPL profile included Lupus anticoagulant, (LA), anti-cardiolipin (aCL), and anti-ß2 glycoprotein I (anti-ß2GPI) antibodies. Plasma samples were tested for the presence of LA according to the recommended criteria from the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies [11,12]. The aCL and anti-ß2GPI were detected by ELISA according to manufacturer's indication (Inova Diagnostics, Inc. San Diego, CA, USA).

3. Results

This retrospective study included 6 consecutive PAPS patients [median age 49.5 (range 38-66), all female] who presented with severe thrombocytopenia (platelets < 50.000/mm^3, mean value 31.000±9.000/mm^3). *Table 1* summarizesthe characteristics of the PAPS patients included in the study. Previous therapy included intravenous immunoglobulins (4 patients) and high doses of steroids (>30 mg/day of prednisone or equivalent [15];3 patients). One

patient received RTX as rescue therapy as a steroid-sparing agent because of the high cardiovascular risk (high body mass index, not-controlled blood pressure, diabetes).

We observed a full response (platelets>150.000/mm^3) to RTX in 5 out of 6 patients (83.3%), achieved in a median of 4 weeks (range 2-6) after last infusion of RTX. One patient did not respond to the B-cell depletion therapy and was treated with a splenectomy one month after RTX therapy and platelets levels normalized after 3 months. Graph 1 summarizes platelets levels before and after RTX treatment. After a median follow-up of more than 4 years, we observed a median time free from relapse of 43 months (range 12-97). No adverse events were reported, no patients developed serious infections, as per FDA definition of serious adverse event [16].

Importantly, the patients required no further maintenance therapy for the thrombocytopenia.

B-cell depletion was seen in patients during a median of 11.6 months (range 6-13).

4. Discussion

As aPL play a pivotal role in the pathogenesis of APS andare produced by B cells, B cell-targeted therapies are of interest in the management of APS. Despite the lack of randomizedcontrolled trials, human and murine studies showthat in APS, B cell-directed therapies may have beneficialclinical and serological effects[17]. The experience of Bcell-directed therapies in patients with APS is limited to RTX only and consists of case reports/series[17,18] and one phase II pilot study[3]. Most of those reports demonstrated a complete to partial response in patients with APS-associated thrombocytopenia treated with RTX[19]. However, long term data on patients' response and the overall efficacy of RTX alone for the management of severe thrombocytopenia in PAPS were still elusive.

In our experience, more than 80% of patients treated with RTX alone did not suffer for any relapse during a median follow-up of 43 months, despite the absence of any maintenance

therapy. Interestingly, among responders, all patients responded within 4 to 6 weeks (early responders).

The usage of RTX in APS-associated thrombocytopenia is extrapolated from ITP experience. RTX has been used off-label in patients with idiopathic thrombocytopenic purpura (ITP) for more than 10 years. Meta-analysis of the heterogeneous studieswith RTX in ITP patients showed that approximately 40–60% of the patients had a response (platelet count >30.000/mm^3) at one year, and 20–25% of those had long-term responsesafter 5 years [20].

RITAPS [3] (RTX in antiphospholipid syndrome) was an open-label phase II study where patients with persistently positive aPL and anticoagulant-resistant manifestations of APS were enrolled. The secondary objective of the trial was to evaluate the effect of the drug on non-criteria manifestations of APS and it showed that out of 4 patients for whom the indication was APS-associated thrombocytopenia, one exhibited a complete response, one partial response, and 2 no response at 24 weeks. Our findings further support the efficacy of B-cell depletion therapy for the management of thrombocytopenia, also in severe cases, showing that a complete long term remission after can be achievedwith RTX alone, even without any further maintenance therapy.

Besides, our observations envisage the role of RTX as a steroid sparing agent in the management of patients with PAPS and concomitant severe thrombocytopenia, as shown in other autoimmune-conditions[21,22].

We acknowledge few limitations for our study. Firstly, the small number of patients and the retrospective design might influence the reproducibility of the results and further prospective analysis to confirm our findings is highly needed. However, one should consider the fact that APS is a rare condition and severe thrombocytopenia presents just in a small subset of APS patients.

5. Conclusion

In one of the longest-term observation (median 46 months) studies, sustained clinical remission without immunosuppressive maintenance therapy was obtained by RTX alone in patients with primary APS and severe thrombocytopenia intolerant or refractory to conventional therapy.

6. References

[1] Radin M, Cecchi I, Schreiber K, Baldovino S, Rossi D, Menegatti E, 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.

[2] Kallenberg CGM. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol 2014;10:484–93. doi:10.1038/nrrheum.2014.104.

[3] Erkan D, Vega J, Ramón 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. doi:10.1002/art.37759.

[4] Erre GL, Pardini S, Faedda R, Passiu G. Effect of rituximab on clinical and laboratory features of antiphospholipid syndrome: a case report and a review of literature. Lupus 2008;17:50–5. doi:10.1177/0961203307085251.

[5] Massimo Radin, Michelle Remião Ugolini-Lopes, Savino Sciascia DA. Extra-criteria manifestations of antiphospholipid syndrome: Risk assessment and management. Semin Arthritis Rheum n.d.:DOI:10.1016/j.semarthrit.2017.12.006.

[6] Sciascia S, Amigo M-C, Roccatello D, Khamashta M. Diagnosing antiphospholipid syndrome: “extra-criteria” manifestations and technical advances. Nat Rev Rheumatol 2017. doi:10.1038/nrrheum.2017.124.

[7] Atsumi T, Furukawa S, Amengual O, Koike T. Antiphospholipid antibody associated thrombocytopenia and the paradoxical risk of thrombosis. Lupus 2005;14:499–504. doi:10.1191/0961203305lu2145rr.

[8] Rudnicka D, Oszmiana A, Finch DK, Strickland I, Schofield DJ, Lowe DC, et al. Rituximab

causes a polarization of B cells that augments its therapeutic function in NK-cell-mediated antibody-dependent cellular cytotoxicity. Blood 2013;121:4694–702. doi:10.1182/blood-2013-02-482570.

[9] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, 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.

[10] Williamson DR, Albert M, Heels-Ansdell D, Arnold DM, Lauzier F, Zarychanski R, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. Chest 2013;144:1207–15. doi:10.1378/chest.13-0121.

[11] Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 1995;74:1185–90.

[12] PENGO V, TRIPODI A, REBER G, RAND JH, ORTEL TL, GALLI M, et al. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009;7:1737–40. doi:10.1111/j.1538-7836.2009.03555.x.

[13] Harris EN, Gharavi AE, Patel SP HG. Evaluation of the anti-cardiolipin antibody test: report of an international workshop held 4 April 1987. Clin Exp Immunol 1986;68:22.

[14] Amengual O, Atsumi T, Khamashta MA, Koike T, Hughes GR. Specificity of ELISA for antibody to beta 2-glycoprotein I in patients with antiphospholipid syndrome. Br J Rheumatol 1996;35:1239–43.

[15] Buttgereit F, Straub RH, Wehling M, Burmester G-R. Glucocorticoids in the treatment of

rheumatic diseases: an update on the mechanisms of action. Arthritis Rheum 2004;50:3408–17. doi:10.1002/art.20583.

[16] Commissioner O of the. Reporting Serious Problems to FDA - What is a Serious Adverse Event? n.d.

[17] Artim-Esen B, Diz-Küçükkaya R, İnanç M. The Significance and Management of Thrombocytopenia in Antiphospholipid Syndrome. Curr Rheumatol Rep 2015;17:14. doi:10.1007/s11926-014-0494-8.

[18] Ramos-Casals M, García-Hernández FJ, de Ramón E, Callejas JL, Martínez-Berriotxoa A, Pallarés L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol n.d.;28:468–76.

[19] Kumar D, Roubey RAS. Use of rituximab in the antiphospholipid syndrome. Curr Rheumatol Rep 2010;12:40–4. doi:10.1007/s11926-009-0074-5.

[20] Godeau B. B-Cell Depletion in Immune Thrombocytopenia. Semin Hematol 2013;50:S75–82. doi:10.1053/j.seminhematol.2013.03.014.

[21] Roccatello D, Sciascia S, Baldovino S, Rossi D, Alpa M, Naretto C, et al. A 4-year observation in lupus nephritis patients treated with an intensified B-lymphocyte depletion without immunosuppressive maintenance treatment-Clinical response compared to literature and immunological re-assessment. Autoimmun Rev 2015. doi:10.1016/j.autrev.2015.07.017.

[22] Roccatello D, Sciascia S, Rossi D, Alpa M, Naretto C, Radin M, et al. The "4 plus 2" rituximab protocol makes maintenance treatment unneeded in patients with refractory ANCA-associated vasculitis: A 10 years observation study. Oncotarget 2017;8:52072–7. doi:10.18632/oncotarget.18120.

Legend of Tables and Figures

Table 1. Patients with PAPS with extra-criteria manifestations that followed a B-cells depleting protocol from the experience of our centre

Graph 1. Platelets levels before and after RTX treatment

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