Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin

S. Sciascia, O. Giachino, D. Roccatello

Dipartimento di Malattie Rare, Immunologiche, Ematologiche ed Immunoematologiche, Centro Universitario di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID), Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale Torino Nord Emergenza San G. Bosco e Università di Torino, Torino, Italy.

Abstract

Objectives

To investigate the long-term effects of megadoses of intravenous immunoglobulin (IVIG) in a small cohort of patients with relapsing primary APS resistant to conventional treatments.

Methods

Five primary APS patients, 4 women, mean age 45.1 years (range 31–76 years), were considered eligible for IVIG therapy due to relapsing thrombotic events (4 recurrent venous thromboses, 2 ischaemic cerebral strokes, 2 pulmonary thrombo-embolisms, 1 thrombotic event on the vena cava filter), despite conventional therapy with anticoagulants. All patients had anti-nuclear antibodies at low-medium titre without other signs or symptoms of systemic lupus erythematosus. IVIG was combined with hydroxychloroquine and, in patients with cerebral strokes, acetylsalicylic acid. Three consecutive daily infusions of IVIG were administered intravenously at a dose of 0.4 g/kg/day every month for 3 months, followed by a single monthly infusion for 9 months.

Results

No further thromboses occurred in the 5 treated patients (mean follow-up 89.2 months, range 61–114). Visual analogue score (VAS 0–10) improved (mean 3.5, range 3.0–5.0, before, and 7.35, range 9.9–6.0, p=0.05) after IVIG treatment.

Conclusion

In a long-term (>5 years) open study in a small cohort of high risk primary APS patients, IVIG was found to be effective in preventing recurrent thrombosis. Full understanding of the mechanisms and efficacy, as well as the optimal doses of IVIG in APS patients with recurrent thrombosis, will require appropriately designed clinical studies. Presently, IVIG use is restricted by costs and limited availability.

Key words

antiphospholipid syndrome, relapsing thrombotic events, intravenous immunoglobulin

Savino Sciascia, MD
Osvaldo Giachino, MD
Dario Roccatello, MD

Please address correspondence to:
Dario Roccatello, MD,
Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare, Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale Torino Nord Emergenza San G. Bosco e Università di Torino, Piazza del Donatore di Sangue 3, 10154 Torino, Italy.
E-mail: dario.roccatello@unito.it

Received on August 5, 2011; accepted in revised form on October 27, 2011.

Competing interests: none declared.

Introduction

Traditionally, anticoagulation has been the treatment of choice for thrombosis associated with antiphospholipid syndrome (APS). In the presence of an appropriate anticoagulation regimen, the risk of recurrent deep vein thrombosis is low. When thrombotic events relapse despite standard treatment, prognosis is poor and there are few therapeutic alternatives. Prednisone, cyclophosphamide, and plasmapheresis have been used with unpredictable success (1).

The beneficial effect of IVIG in APS has been demonstrated in animals (2).

Data on the use of intravenous immunoglobulin (IVIG) in patients with APS are mainly limited to obstetric complications. Few case reports involving other clinical manifestations have been published (3, 4).

The present open prospective study focuses on the long-term effects of megadoses of IVIG in a small cohort of patients with relapsing primary APS and low-medium titre of anti-nuclear antibodies (ANA) resistant to conventional treatments.

Patients and methods

Baseline data are summarised in Table I. Five patients, 4 females, mean age 41.5 years (range 31–76 years), with previously documented thrombosis in primary APS (1 arterial, 4 venous) were considered eligible for IVIG therapy due to relapsing thrombotic events (4 recurrent venous thromboses, 2 ischaemic cerebral strokes associated with hemiparesis, 2 pulmonary thrombo-embolisms, 1 thrombotic event on the vena cava filter) despite conventional therapy with anticoagulants.

All 5 patients complained of mild arthralgia in their hands or knees, though with no tissue swelling or synovitis, and were given hydroxychloroquine (HCQ). They had moderate positivity for ANA (Table I). Neither anti-doublestrand DNA nor anti-Sm were detected. No clinical signs or symptoms of systemic lupus erythematosus could be found. All 5 patients had a high risk aPL profile, according to APS Risk Scale (5).

International normalised ratio (INR) value at the time of recurrence and the mean value of INR in the three months before the thrombosis are shown in Table I.

Additional thrombotic risk factors including hypertension (systolic >140, diastolic >90), hypercholesterolaemia (>240 mg/dl), BMI >85th percentile, pill/hormone replacement therapy, diabetes mellitus, pregnancy or surgery procedure in the period of recurrences were investigated (Table II). Of note, all the patients underwent a screening for inherited thrombophilia. None of them referred sign or symptoms compatible with any oncologic disease during the follow-up.

Three consecutive daily infusions of IVIG were administered intravenously at a dose of 0.4 g/kg/day every month for 3 months, followed by a monthly infusion of 0.4 g/kg/day for 9 more months.

This scheme was derived from our clinical experience in other immune-mediated as systemic lupus erythematosus. Ongoing therapy at the time of relapses is shown in Table I.

IVIG therapy was started in 4 of the 5 (n. 2, 3, 4, 5) patients after a third thrombotic event, which occurred despite the ongoing therapy (Table I).

Patient n. 1 received IVIG therapy after the first recurrence because of a very poor compliance to any medical treatment leading to the inability of the oral anticoagulation therapy (OAT) to maintain INR within the therapeutic range.

The patients routinely attended our clinic in a regular 2-week follow-up. They were evaluated for any thrombotic recurrences and instrumental investigations (including venous Doppler ultrasonography, magnetic resonance imaging, CT scan or lung scintigraphy) were performed as appropriate if any signs or symptoms of recurrence were noted. Response was also evaluated by assessing the changes in clinical signs and symptoms (as well as by the visual analogue score). The thrombosis-free survival were estimated using the Kaplan-Meier method.

Laboratory measurement of aPL (lupus anticoagulant, anticardiolipin and anti-β2glyco-protein I antibodies) was performed in order to evaluate changes in aPL profile following IVIG therapy.

Due to the small number of patients, mainly descriptive statistical analyses

Table I. Demographic and clinical characteristics of APS patients.

Patient	Age(yrs)/ gender	Thrombotic event at onset	Ongoing therapy at the time of relapse	Relapsing thrombotic events	Thrombosis-free time (months)	IVIg indication	ANA (title) IF	aPL profile	INR at the time of recurrences	Mean INR value in the three months before the recurrence Mean (range)
1	38/M	DVT	OAT, HCQ	Pulmonary thrombo-embolism	61	compliance	1:160	High risk	1.87	1.76 (1.2–2.99)
2	54/F	DVT	OAT, HCQ	DVT + pulmonary thrombo-embolism	90	Relapsing despite ongoing therapy	1: 320	High risk	2.42 (second event) 2.74 (third event)	2.37 (2.12–3.10) 2.65 (2.23–3.20)
3	76/F	DVT	OAT, ASA, HCQ	Stroke, thrombosis of vena cava filter	114	Relapsing despite ongoing therapy	1:160	High risk	2.57 (second event) 3.18 (third event)	2.61 (2.00–3.41) 2.71 (2.34–3.32)
4	72/F	DVT	ASA, OAT, HCQ	DVT, stroke	90	Relapsing despite ongoing therapy	1:160	High risk	2.83 (second event) 2.63 (third event)	2.33 (1.86–2.98) 2.77 (1.54–3.78)
5	31 /F	stroke	ASA, OAT, HCQ	DVT (2 events)	91	Relapsing despite ongoing therapy	1:80	High risk	2.27 (second event) 2.34 (third event)	2.12 (1.95–2.76) 2.23 (1.99–2.88)

DVT: deep vein thrombosis; OAT: oral anticoagulant therapy; HCQ: hydroxychloroquine; ASA: acetylsalicylic acid; IF immunofluorescence; aPL profile is defined according to Sciascia S, Cosseddu D, Montaruli B, Kuzenko A, Bertero MT. Risk Scale for the diagnosis of antiphospholipid syndrome. *Ann Rheum Dis* 2011; 70: 1517-8.

were performed. Variables were analysed by multifactorial ANOVA or non-parametric statistical methods (Spearman's rank correlation test and Wilcoxon test). Differences were considered statistically significant when two-sided *p*-values were <0.05. Statistical analyses were carried out using StatView 5.0.1 for Macintosh (SAS institute, Cary, NC, USA).

Results

No further clinical or instrumental-proven thromboses occurred in the 5 treated patients (mean follow-up 89.2 months, range 61–114). Visual analogue score (VAS 0–10) ameliorated, mean 3.5 (3.0–5.0) before and 7.35 (9.9–6.0, p=0.05) after IVIG treatment. Event profile survival in patients before and after IVIG treatment is shown in Figure 1.

Despite clinical improvement no statistically significant differences were observed in the aPL profile prior to and after IVIG treatment measured at 6, 12 and 24 months.

Discussion

Several *in vivo* and *in vitro* models have demonstrated that IVIG in APS blocks autoantibodies increases the clearance of pathologic IgG, modulates complement, protects against autoantibody-mediated pathology by up-regulating an inhibitory Fcγ receptor on macrophages, and suppresses pathogenic cytokines.

Infusion of IVIG in diseased animals resulted in significantly fewer foetal resorptions as compared to untreated mice (6). Similar results were obtained with IVIG treatment of experimentally induced systemic lupus erythematosus and primary APS (7).

To our knowledge, the first report of IVIG use in APS was probably the one by Carreras *et al*. (8), and it referred to recurrent pregnancy loss. After this study, several other cases of successful pregnancy outcome in APS patients with previously recurrent miscarriages were reported.

Administration of IVIG has been taken into consideration for the treatment of catastrophic APS as well (9).

These were the reasons why IVIG was

Table II. Thrombotic risk factors (acquired and inherited).

Patient	Thrombotic risk factors
1	Smoking
2	Hypertension, pharmacological treated after the first recurrence
3	Age >70 years old
4	Ex-smoker, heterozigosis for factor V Leiden
	Age >70 years old
5	–

This research received no specific grant from any funding agency in the public, commercial, or non-profit sectors.

administered to our patients. The long thrombosis-free interval (mean 89.2 months) confirms the strength of our working hypothesis.

Treatment of recurrent thrombotic events in APS is still a challenge. The first step in the management of APS patients who have recurrent events despite therapeutic anticoagulation therapy is to identify and possibly reduce the non-aPL risk factors for thrombosis. There are quite a number of possible second steps, including administering low-dose aspirin or hydroxychloroquine and/or statins, switching to low-molecular-weight heparin, increasing the warfarin dose to achieve a higher INR (*e.g.* INR to 3-4) with or without low-dose aspirin.

All the enrolled patients were given hydroxychloroquine. It is worth pointing out that ANA were positive in all 5 patients. Anti-DNA antibodies and complement (C3 and C4) values were negative or normal, and no signs or symptoms of coexisting lupus-like diseases were detected during follow-up. We could speculate that the presence of ANA in most of these patients with APS may have conferred an increased risk of relapsing thrombosis. More recent concepts such as the primary *plus* APS, denoting APS patients who have one or two clinical manifestations that are not included in the current classification criteria for SLE or any other connective tissue disorder (10), are increasingly being put forth and we hypothesise that this condition may refer to our patients as well. While this immunological profile associated with arthalgia is nondiagnostic for SLE, we felt the use of HCQ to be justified. Furthermore, experimental and clinical evidence has shown that HCQ may decrease the incidence of thrombosis (11). Controlled studies are needed to determine the effectiveness of HCQ in the prevention of primary and secondary thrombosis in APS.

Other approaches using statins or long-term, low-molecular-weight heparin associated with warfarin are mentioned in the literature, but their use is not widely accepted.

Several experts recommend that patients with APS should be treated with warfarin in doses adjusted to achieve an international normalised ratio (INR) ≥3.0, whereas a target INR of 2.0 to 3.0 is generally recommended for patients who do not have aPL (9). This recommendation is mainly based on retrospective (12), nonconsecutive case studies but it is a matter of fact that patients with higher INR values bleed more frequently than patients with lower INR values. Finally, two prospective, randomised, controlled trials using two different intensities of warfarin therapy concluded that both moderate (INR 2–3) and high- intensity (INR 3–4) anticoagulation are similarly protective in APS patients after the first thrombosis (13, 14).

The doses and protocols used in the present study were derived from our anecdotal experience in other immune-mediated disorders. Cumulative doses were considerably lower than in other schemes, such as the 2g/kg dosage over a 5-day period once a month for 6 months, followed by another administration every 3 months proposed by Zandman-Goddan, Krauthammer and Shoenfeld for steroid-sparing aims in autoimmune diseases (15).

No current guidelines exist as to the duration, frequency, or optimal dose of IVIG. Studies are needed to evaluate these issues as well as the potential role of IVIG in recurrent thrombosis in APS. Presently, IVIG administration may be considered a rescue therapy in selected patients.

We are aware that our patients, all ANA-positive at low-medium titre, though free of other sign of SLE, could represent a subset of cases potentially more susceptible for IVIG therapy. This feature could facilitate identification of potentially responders.

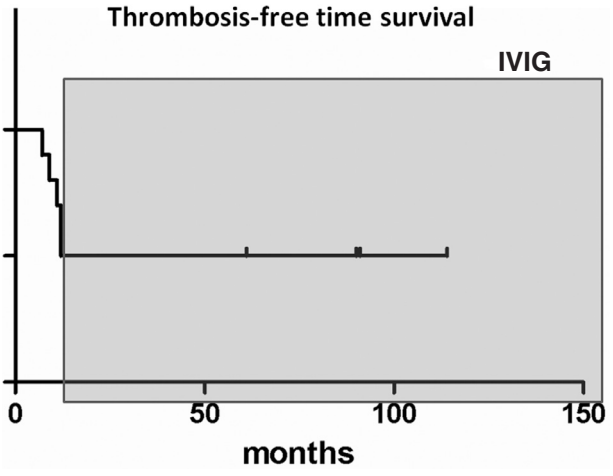

Fig. 1. Thrombosis-free time survival.
Event profile survival in APS patients before and after IVIG treatment. No relapses were observed after IVIG administration (highlighted in the figure) compared to period before IVIG when conventional therapy alone was ongoing (estimated using the Kaplan-Meier method).

Conclusion

In a long-term (>5 years) open study in a small cohort of high risk PAPS patients with detectable ANA, IVIG, in conjunction with hydroxychloroquine, was found to be effective in preventing recurrent thrombosis.

Full understanding of the mechanisms and efficacy, as well as the optimal doses of IVIG in APS patients with recurrent thrombosis will require appropriately designed clinical studies. Presently, IVIG use is restricted by costs and limited availability.

References

1. RUIZ-IRASTORZAG, CROWTHER M, BRANCH W, KHAMASHTA MA: Antiphospholipid syndrome. *Lancet* 2010; 376: 1498-509.
2. BAKIMER R, GUILBURD B, ZURGIL N, SHOENFELD Y: The effect of intravenous gamma-globulin on the induction of experimental antiphospholipid syndrome. *Clin Immunol Immunopathol* 1993; 69: 97-102.
3. HSIAO GR, WOLF RE, KIMPEL DL: Intravenous immunoglobulin to prevent recurrent thrombosis in the antiphospholipid syndrome. *J Clin Rheumatol* 2001; 7: 336-9.
4. ARABSHAHI B, THOMPSON ED, SMERGEL EM, GOLDSMITH DP: Long-term treatment antiphospholipid syndrome-associated cerebral arterial thromboses with intravenous immunoglobulin: a case report. *Clin Rheumatol* 2007; 26: 251-3.
5. SCIASCIA S, COSSEDDU D, MONTARULI B, KUZENKO A, BERTERO MT: Risk Scale for the diagnosis of antiphospholipid syndrome. *Ann Rheum Dis* 2011; 70: 1517-8.
6. BAKIMER R, GUILBURD B, ZURGIL N, SHOENFELD Y: The effect of intravenous γ-globulin on the induction of experimental antiphospholipid syndrome. *Clin Immunol Immunopathal* 1993; 69: 97-102.
7. KRAUSE I, BLANK M, KOPOLOVIC J *et al*.: Abrogation of experimental systemic lupus erythematosus and primary antiphospholipid syndrome with intravenous gammaglobulin. *J Rheumatol* 1995; 22: 1068-74.
8. CARRERAS LD, PEREZ GN, VEGA HR, CASAVILLA F: Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. *Lancet* 1988; 13: 393-4.
9. PALOMO I, SEGOVIA F, ORTEGA C, PIERANGELI S: Antiphospholipid syndrome: a comprehensive review of a complex and multisystemic disease. *Clin Exp Rheumatol* 2009; 27:668-77.
10. ASHERSON RA, SCHAMROTH-RAPAPORT N, SKUDOWITZ B *et al*.: Recurrent deep vein thrombosis, ovarian carcinoma and antibodies to mitochondria M5 in a patient with asymptomatic Primary ''plus'' antiphospholipid syndrome: an unusual combination. *Clin Exp Rheumatol* 2007; 25: 890-5.
11. PIERANGELI SS, ERKAN D: Antiphospholipid syndrome treatment beyond anticoagulation: are we there yet? *Lupus* 2010; 19: 475-85.
12. KHAMASHTA MA, CUADRADO MJ, MUJIC F, TAUB NA, HUNT BJ, HUGHES GR: The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; 332: 993-7.
13. CROWTHER MA GINSBERG JS, JULIAN J *et al*.: Comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 2003; 349: 1133-8.
14. FINAZZI G, MARCHIOLI R, BRANCACCIO V *et al*.: A randomized clinical trial of high-intensity warfarin vs conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost* 2005; 3: 848-53.
15. ZANDMAN-GODDARD G, KRAUTHAMMER A, SHOENFELD Y: The steroid sparing effect of IVIG. *Exper Rev Clin Immunol* 2007; 3: 773-80.