CONCISE REPORT

Treatment of severe thrombocytopenia in systemic lupus erythematosus with intravenous gammaglobulin

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Abstract

Three patients with lupus with severe autoimmune thrombocytopenia were treated with high doses of intravenous gammaglobulin. In the patient with active disease a prolonged but partial response with respect to platelet counts was observed. In the two other patients who had no disease activity other than thrombocytopenia at the time of intravenous gammaglobulin treatment a minor (and only transient) increase in platelet counts was seen after treatment. No change in the state of disease activity nor in the levels of antinuclear antibodies, circulating immune complexes, nor complement C3/4 was observed in these three patients after treatment with intravenous gammaglobulin.

(*Ann Rheum Dis* 1992; 51: 1149–1151)

Severe autoimmune thrombocytopenia occurs in 5–10% of patients with systemic lupus erythematosus (SLE). Corticosteroids are recommended for its treatment, with cytostatic drugs or splenectomy if remission is not achieved. Owing to the known side effects of corticosteroids and cytostatic drugs and the hazards of splenectomy alternative treatments have been sought. In 1981 Imbach *et al* reported the successful treatment of severe refractory childhood idiopathic thrombocytopenic purpura with high doses of gammaglobulin, which has no appreciable side effects.[1] The efficacy of intravenous gammaglobulin treatment of thrombocytopenia has also been reported in adults for acute and chronic idiopathic thrombocytopenic purpura.[2] Some papers have reported beneficial effects of intravenous gammaglobulin on thrombocytopenia in a small number of patients with SLE.[3–5] Another report, however, showed no effect of intravenous gammaglobulin on thrombocytopenia in a patient with SLE.[6] The underlying mechanism of improvement of thrombocytopenia after intravenous gammaglobulin is not completely understood but inhibition of the Fc receptor mediated destruction of antibody coated platelets by the mononuclear phagocyte system[2 7] and downregulation of the autoantibody response[8] have been proposed. We treated three adult patients with SLE with severe immune mediated thrombocytopenia with intravenous gammaglobulin and evaluated the clinical results and the effects on levels of circulating immune complexes and autoantibodies.

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Accepted for publication 21 May 1992

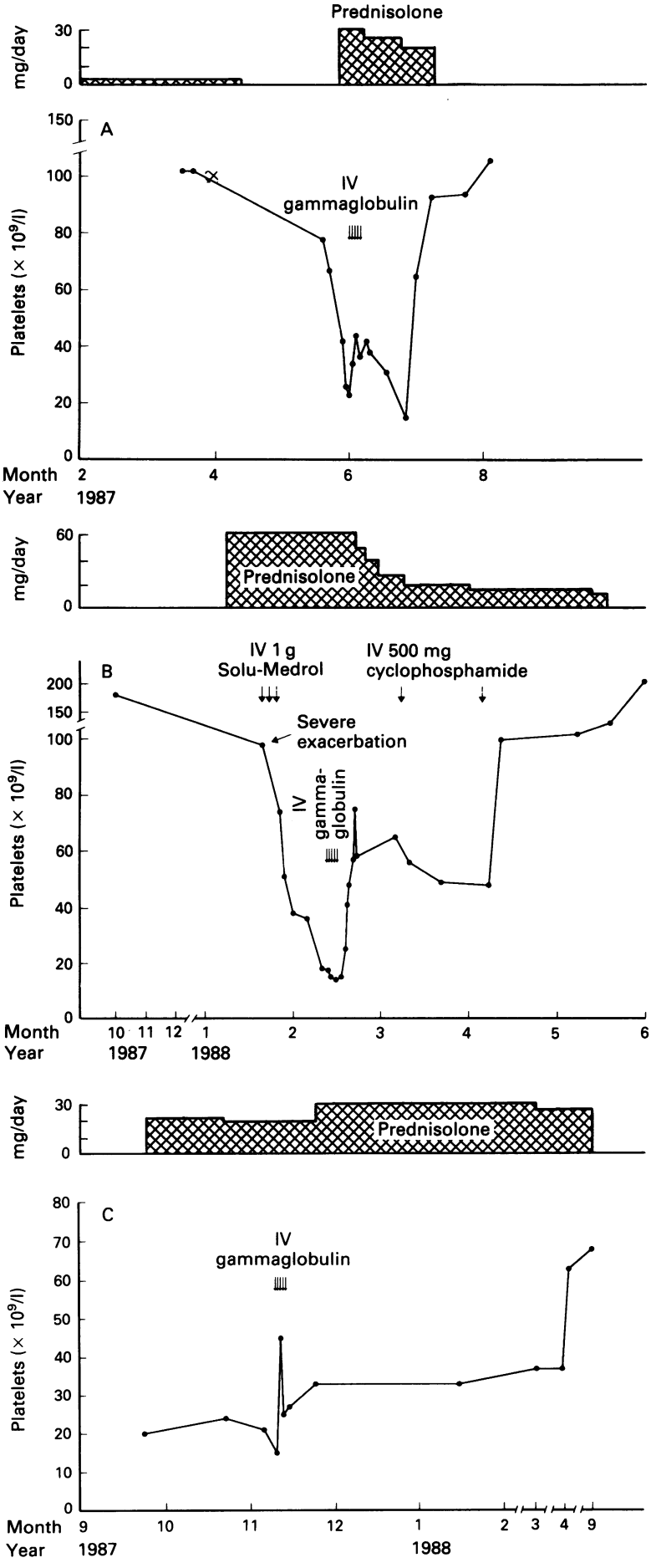
Patients and methods

PATIENTS

Three consecutive (female) patients with severe autoimmune mediated thrombocytopenia (platelet counts $<30\times10^9$/l) and fulfilling the 1982 revised American Rheumatism Association criteria for establishing the diagnosis of SLE were included. The table gives the clinical characteristics at the start of the study. None of the patients had evidence of disseminated intravascular coagulation. At the beginning of treatment with intravenous gammaglobulin only patient B had signs of haemolytic anaemia whereas patients A and C had leucopenia. Patients A and B had recent onset thrombocytopenia whereas patient C had longstanding thrombocytopenia. Reasons for treatment with intravenous gammaglobulin were multiple (relative) contraindications for corticosteroids in patient A, unresponsiveness to high doses of prednisolone (60 mg/day) in patient B, and refusal to take a higher dose of prednisolone in patient C. None of the patients had bleeding disorders at the time of intravenous gammaglobulin treatment.

Demographic data, cumulative American Rheumatism Association (ARA) criteria for the classification of systemic lupus erythematosus (SLE)[13] and additional data at the start of treatment with intravenous immunoglobulin in three patients with SLE and severe thrombocytopenia

Characteristics	*Patient*		
	A	*B*	*C*
Age (years)	44	36	27
Duration of SLE (years)	9	10	12
Cumulative ARA criteria			
Malar rash	–	–	–
Discoid rash	–	–	–
Photosensitivity	–	–	+
Mouth ulceration	–	–	–
Arthritis	+	–	+
Serositis	–	–	+
Renal disease	–	+	–
Neurological disease	–	–	+
Haemolytic anaemia	–	+	+
Leucopenia	+	+	+
Lymphopenia	+	+	+
Thrombocytopenia	+	+	+
Antibodies to Sm (CIE)	+	–	–
Lupus erythematosus cell preparation	+	+	+
Antibodies to double stranded DNA	–	+	+
False positive serological test for syphilis	–	–	–
Antinuclear antibodies ($\geq$1:40)	+	+	+
Additional data			
Lupus anticoagulant activity	–	+	+
Anticardiolipin antibodies			
IgG	–	–	–
IgM	+	–	–
Duration of thrombocytopenia before intravenous gammaglobulin			
$<30\times10^9$/l (days)	2	4	48
$<100\times10^9$/l (weeks)	2	5	117



Course of platelet counts before, during, and after infusion of gammaglobulin in (A) patient A; (B) patient B; and (C) patient C.

STUDY DESIGN

The patients received intravenous gammaglobulin (Central Laboratory of the Blood Transfusion Service, Amsterdam), 0·4 g/kg body weight, on five consecutive days. From days 0 to 5 haemoglobin levels, white blood cell and platelet counts were measured daily and thereafter at frequent intervals. Just before gammaglobulin infusion (day 0) and on days 5, 10, and 24 the following laboratory tests were performed: levels of antinuclear antibodies, antibodies to double stranded DNA, IgG, IgM, IgA, C3/C4, and circulating immune complexes. In addition, just before and on day 10 antiplatelet antibodies were determined in serum samples.

METHODS

Antinuclear antibodies and antibodies to double stranded DNA were determined by indirect immunofluorescence using human fetal fibroblasts and *Crithidia luciliae* respectively as a substrate. IgG (normal value 8·5–15·0 g/l), IgA (normal value 0·9–4·5 g/l), and IgM (normal value 0·6–2·6 g/l) and complement C3 (normal value 0·64–1·20 g/l) and C4 (normal value 0·11–0·40 g/l) were determined by nephelometry. Circulating immune complexes (normal value <40, on a scale of 0 to >1000 based on IgG containing inclusions) were determined by the indirect granulocyte phagocytosis test.[9]

Results

The effect of intravenous gammaglobulin on platelet counts is shown in the figure. Platelet counts increased in all three patients, starting after one day in patients A and C and after four days in patient B. Peak numbers of platelets were reached at one to seven days. In patient A the increase in platelet counts was temporary and restricted whereas in patients B and C the numbers of platelets remained higher than before intravenous gammaglobulin but were still in the lower range. In patients A and C a good to moderate response with respect to platelet counts was observed after starting treatment with prednisolone or increasing the dose of prednisolone respectively. In patient B the addition of intravenous cyclophosphamide was accompanied by a further increase in the platelet count. Haemoglobin concentrations did not increase and the white blood cell count did not change after treatment with intravenous gammaglobulin. With respect to immunological parameters, an increase was observed in IgG concentrations (as expected) but levels of antinuclear antibodies, circulating immune complexes and complement C3/4 did not change. Antiplatelet antibodies could not be detected in serum samples before or after treatment with intravenous gammaglobulin.

Discussion

We evaluated the effect of intravenous gammaglobulin treatment in three adults with SLE and severe autoimmune thrombocytopenia. In two patients a rapid but slight and only temporary

increase in platelet counts was observed whereas in the other patient a slow but more substantial and persistent increase in platelet counts was seen. Adults with chronic idiopathic thrombocytopenic purpura are reported to respond with an immediate increase in platelet counts but the long term results are generally discouraging. The platelet response in patients with SLE was found to be similar to that in adults with idiopathic thrombocytopenic purpura.[7]

Transient blockade of the mononuclear phagocyte system seems to be the best explanation for the initial response of thrombocytopenia.[2] In patients with lupus with active disease the mononuclear phagocyte system function has been reported to be defective.[10] Intravenous gammaglobulin treatment in such patients cannot possibly block the mononuclear phagocyte system further. This might explain the absence of an immediate increase in platelet counts in patient B, who had active disease, in contrast to the immediate response in patients A and C who had no evidence of disease activity other than thrombocytopenia.

The long term response after treatment with intravenous gammaglobulin in some patients requires another explanation and may be due to a more specific immunosuppressive or down-regulatory effect of exogenous gammaglobulin on antibody production. Bussel *et al* have suggested that the response of platelet counts to intravenous gammaglobulin is correlated with the amount of inhibition of antiplatelet antibody production,[8] probably due to anti-idiotypic suppression of autoantibody formation. Indeed, Tsubakio *et al* reported a decreased non-specific immunoglobulin production in pokeweed mitogen stimulated lymphocyte cultures after gammaglobulin infusions in patients with idiopathic thrombocytopenic purpura.[11] After gammaglobulin treatment several autoantibodies, including antinuclear antibodies and antibodies to double stranded DNA, were found to be decreased.[12] We, however, did not find any change in levels of these antibodies after treatment with intravenous gammaglobulin. This does not support the concept of anti-idiotypic suppression of intravenous gammaglobulin.

In addition to effects on humoral immunity, changes in cellular immunity have been reported after treatment with intravenous gammaglobulin. Delfraissy *et al* reported enhancement of T suppressor cell function after treatment with intravenous gammaglobulin whereas no change in T cell subsets was recorded.[13] In patients with Kawasaki disease non-specific immunosuppression was demonstrated after treatment with intravenous gammaglobulin, including a decrease in the number of T helper cells and an increase in the number of T suppressor cells.[14]

A reduction in circulating immune complexes has also been found after treatment with intravenous gammaglobulin.[4] This could not be confirmed in another study.[5] We did not find any decrease in levels of circulating immune complexes or an increase of C3/C4 after intravenous gammaglobulin treatment. These levels, however, were in the normal range before treatment with intravenous gammaglobulin. Winiarski *et al* suggested that the effect of treatment with intravenous gammaglobulin on thrombocytopenia might be due to the interference with antiplatelet antibody binding to platelets.[15] We did not find antiplatelet antibodies in the serum samples either before or after treatment with intravenous gammaglobulin. Unfortunately, we did not investigate the presence of platelet bound antiplatelet antibodies before and after treatment with intravenous gammaglobulin. No common agreement exists with respect to the explanation for the long term response of thrombocytopenia after treatment with intravenous gammaglobulin.

In conclusion, in contrast with the treatment of idiopathic thrombocytopenic purpura, intravenous gammaglobulin seems to be of limited value in the treatment of SLE associated thrombocytopenia.

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