Blut (1986) 52: 117–121

Blut

Efficacy of Rhesus Antibodies (Anti-Rh_0(D)) in Autoimmune Thrombocytopenia: Correlation with Response to High Dose IgG and the Degree of Haemolysis

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Summary. We have compared the efficacy of high-dose IgG with that of Rhesus antibodies (anti-Rh_0(D)) in 5 patients with autoimmune thrombocytopenic purpura (3 adults and 2 children). Although only transient, high-dose IgG (0.4 g/kg × 5 days) was effective in all patients (peak values $50-200\times10^9$/l), whereas anti-Rh_0(D) (11–20 µg/kg × 5 days) led to comparable results in only 3 patients (165×10^9/l, 72×10^9/l, 33×10^9/l). This response to anti-Rh_0(D) was neither related to the degree of induced haemolysis (increase of LDH and decrease of haptoglobin) nor to the amount of IgG antibodies bound to red blood cells, as quantified by the 125-I-antiglobulin test. A decrease of platelet-associated IgG was recorded in 3 patients: 2 of them showed an improvement of platelet counts and in one of them there was no response.

We conclude that the therapeutic response of high-dose IgG and anti-Rh_0(D) is independent of the degree of induced haemolysis and may not be predicted from the effectiveness of either therapy alone.

Key words: Autoimmune thrombocytopenic purpura – High-dose IgG treatment – Anti-Rh_0(D) treatment

Autoimmune thrombocytopenic purpura (AITP) is a benign bleeding disorder which generally does not require treatment. In case of haemorrhage or of scheduled surgery, however, a rapid rise of platelet counts is necessary to improve haemostatic competence. Traditionally steroids have been administered for this purpose. Only recently has it been established that high-dose IgG may also be effective [1–3], within an even shorter time.

One hypothesis suggests that high-dose IgG induces clinically inapparent haemolysis [5] which then may prevent platelet destruction by competitive blockade of the reticuloendothelial system. Therefore, Rhesus antibodies (anti-Rh_0(D)) have also been used and have been found effective in 6 out of 10 patients treated so far [6].

We have studied the efficacy of anti-Rh_0(D) after successful high-dose IgG treatment in 5 patients and have related the degree of treatment-induced haemolysis to the platelet increase.

Patients and Methods

Five Rhesus positive patients with AITP – 3 adults and 2 children – who were successfully treated with high-dose IgG 3–6 weeks previously, were selected for anti-Rh_0(D) treatment. The chronic form of AITP was supported by a disease duration of more than 6 months in all patients. All of them presented with bleeding tendency (i.e. petechias) or haematomas. The clinical data and the response to previous treatment are summarized in Table 1. One patient had been splenectomized 10 years earlier with only a transient improvement. Patients received high-dose IgG (0.4 g/kg body weight on five consecutive days, Immunglobulin Biochemie®, Biochemie, Vienna, Austria). After return of platelet counts to pretreatment levels, we infused anti-Rh_0(D) (11–20 μg/kg body weight, Anti-Rh_0(D)®, Biotest, Frankfurt/Main, FRG) intravenously for 30 min. This infusion was also repeated on 5 consecutive days according to the high-dose IgG administration protocol.

Blood samples were obtained before anti-Rh_0(D) treatment and daily thereafter, in order to measure platelet counts (phase contrast microscopy) and platelet associated IgG (PAIgG) [4], to perform the direct red blood cell – 125-I antiglobulin test (E-RIAT) [7], and to determine serum haptoglobin and serum lactic dehydrogenase (LDH) concentrations. Samples for the determinations of PAIgG and for the E-RIAT were stored at 4°C and were simultaneously measured in the appropriate assay.

Results and Discussion

The individual therapeutic effect of high-dose IgG and of anti-Rh_0(D) – as evaluated by the platelet increase – is shown in Fig. 1. High-dose IgG induced an elevation of platelet counts in all patients – although it was only moderate in one of them – for more than two weeks. Utilizing anti-Rh_0(D), a similar increase of platelet counts was observed in 3 patients only, and pretreatment levels were regained 10 days after initiation of therapy. These results may be interpreted as high-dose IgG being superior to anti-Rh_0(D). It should be emphasized, however, that – in contrast to the world-wide experience with high-dose IgG – the optimum dosage of anti-Rh_0(D) is still unknown. Thus, although the total dosage of anti-Rh_0(D) was slightly higher in our study, in which the administration protocol resembled that of high-dose IgG, higher dosages of single drug administrations were found to elevate platelets for a longer period [6]. However, the dosages had been adjusted individually and varied within consecutive administrations in this latter study.

In all our patients red blood cells were strongly coated with a comparable amount of IgG as evaluated by the E-RIAT (Table 1). Although we have applied a slightly higher dosage of anti-Rh_0(D) than in the former study [6], no relation between platelet response and the degree of haemolysis – as indicated by an increase of serum LDH concentrations and a decrease of serum haptoglobin values – could be established (Fig. 2). Accordingly, we also have not observed a decrease of haptoglobin in every case with high-dose IgG treatment [3]. The drop of haemoglobin levels was clinically negligible and in neither case was haemolysis a restrictive factor for therapy. This may indicate that the application of even higher dosages of anti-Rh_0(D) may be of therapeutic value.

Levels of PAIgG dropped in 2 "responders" (nos. 1 and 2) and in one anti-Rh_0(D)-refractory patient (no. 5). In the other two patients it did not change. A similar decrease of PAIgG has been reported in patients successfully treated with high-dose IgG [3].

Table 1. Clinical data and laboratory findings in five patients with AITP treated consecutively with high-dose IgG and with anti-Rh_0(D)

patient (No)	age/sex (years)	duration of disease (month)	previous treatment	anti-Rh_0(D) dosage (μg/kg/day)	peak values before/after anti-Rh_0(D) platelets ($\times 10^9$/l)	PAIgG (% radioactivity)	E-RIAT (% radioactivity)
1	58/f	50	Glu	13	5/150	7.4/ 3.7	1.4/10.6
2	74/f	192	Glu, Sp, Aza, Cy, VA	15	7/ 72	20.0/ 4.5	1.5/12.3
3	4/f	7	Glu	20	11/ 33	11.6/10.0	1.3/ 8.6
4	59/m	180	Glu, Aza, VA	11	1/ 4	7.9/ 7.9	0.7/ 6.7
5	14/m	2	Glu	15	4/ 15	8.3/ 3.7	1.3/10.9

normal values of PAIgG: $< 2.5\%$ (as determined in 120 controls)
normal values of E-RIAT: $< 2.3\%$ (as determined in 60 controls)
Abbreviations: Glu glucocorticoids, Sp splenectomy, Aza azathioprine, Cy cyclophosphamide, VA vinca alkaloids

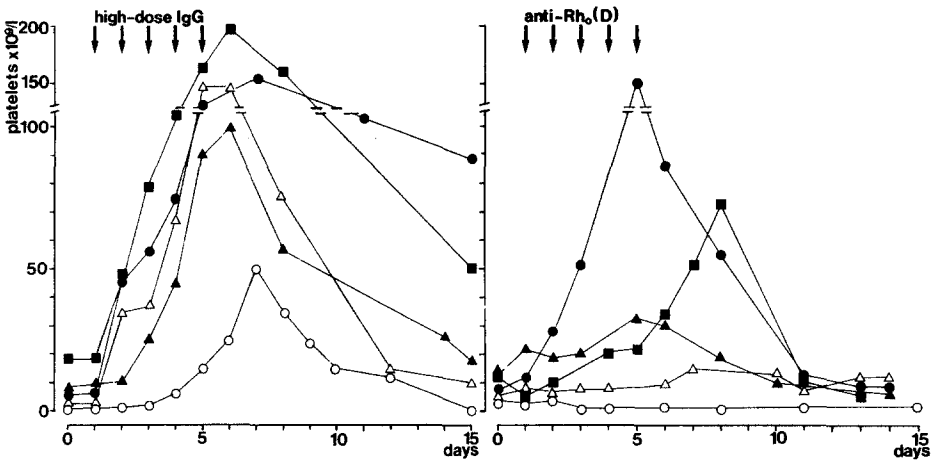

Fig. 1. Individual response of platelet counts in 5 patients with AITP treated with high-dose IgG (left figure) and with anti-Rh_0(D) (right figure). The symbols used denote patient 1 (●), patient 2 (■), patient 3 (▲), patient 4 (○) and patient 5 (△)

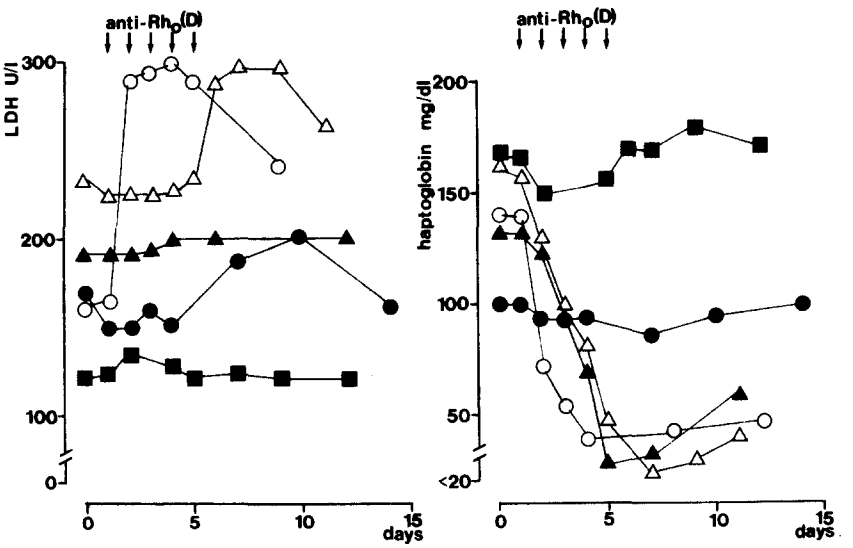

Fig. 2. Serum LDH and haptoglobin levels after treatment with anti-Rh_0(D). Symbols designed as in Fig. 1

We conclude that although both high-dose IgG and anti-Rh_0(D) lead to a coating of red blood cells, the effect on platelet counts may be independent of the degree of the induced haemolysis. To date, no final conclusions concerning the superiority of one or the other immunoglobulin preparations can be drawn from the small number of patients treated, especially as our results may have been biased by the selection of high-dose IgG responders for anti-Rh_0(D) treatment. In view of the high costs of high-dose IgG, anti-Rh_0(D) may be considered as a new therapeutic approach in AITP. It should therefore be compared with high-dose IgG in a prospective study with a larger number of patients.

Acknowledgement. The authors would like to thank Jean E. Haas-Makumbi for editing the manuscript.

References

1. Fehr J, Hofmann V, Kappeler U (1982) Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. N Engl J Med 306: 1254–1258
2. Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, Rossi E, Schöni M, Vest M, Wagner HP (1981) High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet I: 1228–1230
3. Korninger C, Panzer S, Graninger W, Neumann E, Niessner H, Lechner K, Deutsch E (1985) Treatment of severe chronic idiopathic thrombocytopenic purpura in adults with high-dose intravenous gammaglobulin. Scand J Haematol 34: 128–132
4. Mueller-Eckhardt C, Schulz G, Sauer KH, Dienst C, Mahn I (1978) Studies on the platelet radioactive anti-immunoglobulin test. J Immunol Methods 19: 1–11
5. Salama A, Mueller-Eckhardt C, Kiefel V (1983) Effect of intravenous immunoglobulin in immune thrombocytopenia. Competitive inhibition of reticuloendothelial system function by sequestration of autologous red blood cells? Lancet II: 193–195
6. Salama A, Kiefel V, Amberg R, Mueller-Eckhardt C (1984) Treatment of autoimmune thrombocytopenic purpura with Rhesus antibodies (anti-Rh_0(D)). Blut 49: 29–35
7. Schmitz N, Dijbey I, Kretschmer V, Mahn I, Mueller-Eckhardt C (1981) Assessment of red cell autoantibodies in autoimmune hemolytic anaemia of warm type by a radioactive anti-IgG test. Vox Sang 41: 224–230

Received July 3, 1985/Accepted October 11, 1985