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Clinical Effect of Intravenous Immunoglobulin on Chronic Idiopathic Thrombocytopenic Purpura

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Summary. High dose immunoglobulin infusions showed a marked effect on platelet counts in eight out of nine chronic ITP patients and in one SLE patient. In the comparison of different IgG-preparations, the pepsin treated IgG F $(ab')_2$ showed no platelet elevation while the sulfonated did. The elevated platelet count could not be maintained after discontinuation of IgG infusions, but in six out of ten patients the platelet level remained above the pretreatment values. This new treatment seems to be safe and effective in adulthood ITP.

Key words: Idiopathic thrombocytopenic purpura in adulthood – Intravenous immunoglobulin

Introduction

Chronic idiopathic thrombocytopenic purpura (ITP) [1, 2] is a heterogeneous clinical syndrome. Its pathogenesis is not clear but the current therapeutic strategy is to suppress immunological reactions on peripheral platelets. The most widely used drugs for the treatment of ITP are adrenocortical steroids. In some patients, however, these agents induce an unsatisfactory increase in platelet count. Other approaches have therefore been studied [3, 4].

Recently Imbach et al. [5] observed marked increases of platelet counts in children with acute and chronic ITP after transfusing high doses of an intact 7-S IgG [Sandoglobulin (SG) = Immunglobulin SRK]. In our study this proposed mode of treatment was applied to chronic ITP cases in adulthood.

Patients and Methods

Patient's clinical data are given in Figs. 1 and 2. Nine patients with chronic ITP (three male and six female) and one patient with systemic lupus erythematosus (SLE) with thrombocytopenia were considered eligible for the study according to the following criteria: (1) continuous

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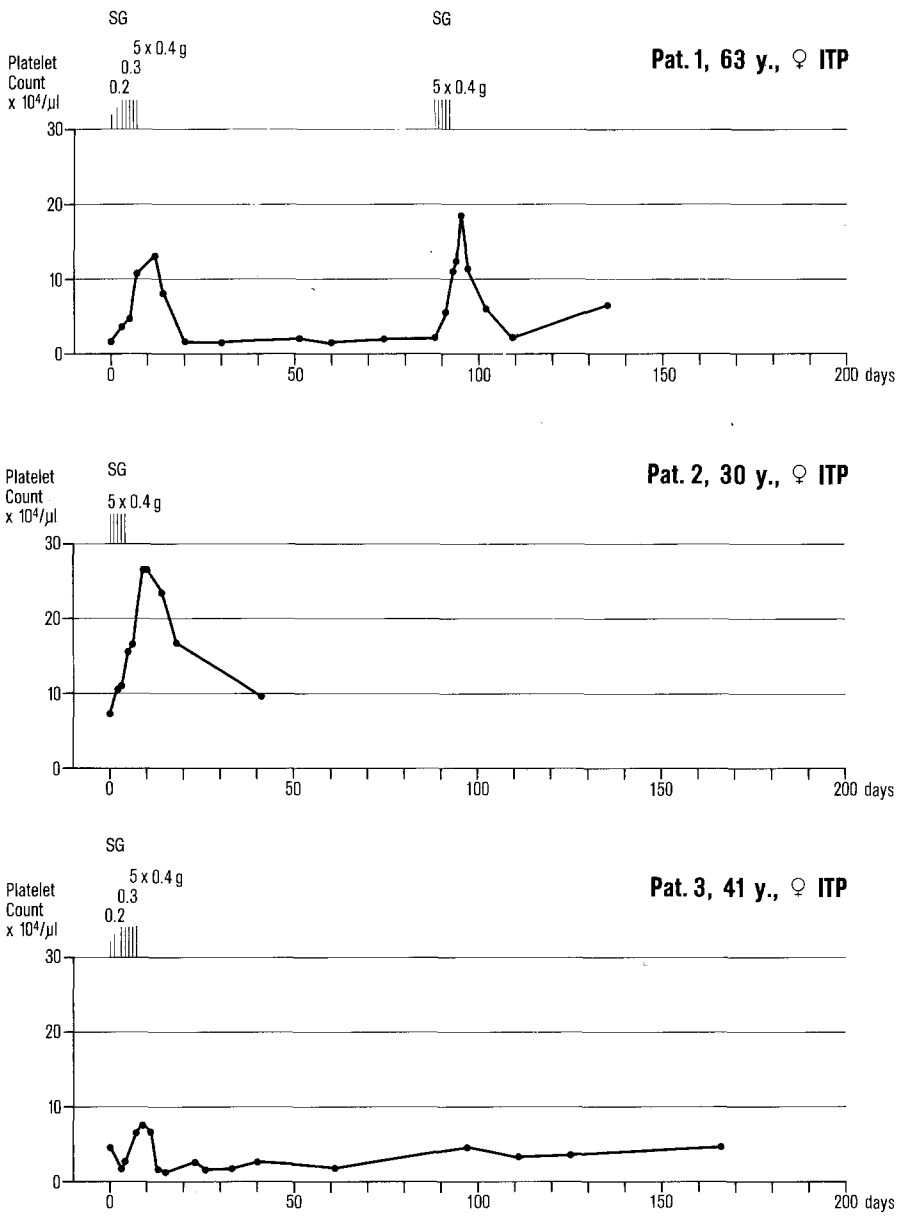

Fig. 1. Variation of platelet count after Sandoglobulin (SG) in patients 1–5. Figures denote g/kg body weight of SG

thrombocytopenia below $10 \times 10^4/\mu l$ for more than one year, (2) range of platelet count within less than 25% of basic platelet count, (3) occasional bleeding tendencies observed as clinical symptoms, (4) known resistance to treatment with adrenocortical steroids, (5) no history of immunodeficiency or idiosyncrasy against immunoglobulin, (6) no other medicaments with possible influence on platelets, (7) no pregnancy.

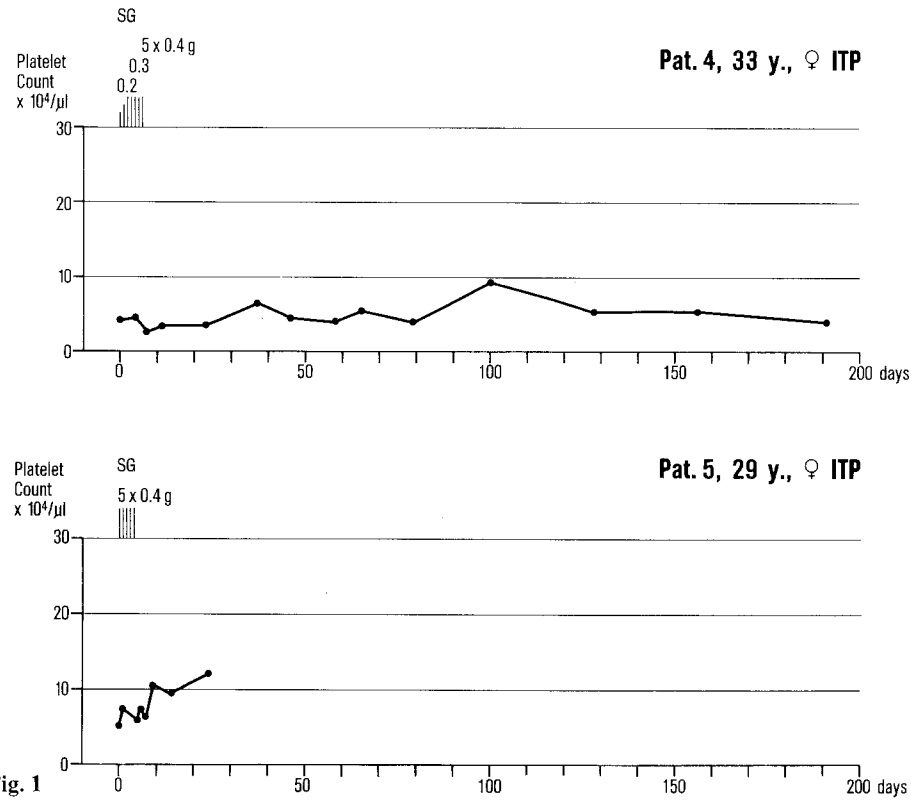

Fig. 1

Human intact immunoglobulin (SG) was employed in all patients. In addition one ITP-patient received modified immunoglobulin preparations (Venilon, Teijin, Japan; Venoglobulin, Green Cross, Japan; Gammavenin, Behring, FRG). These preparations were used according to the instructions of the manufacturers. The solutions were infused intravenously at doses of 0.25 g/kg to 0.4 g/kg body weight for 5–7 days. The course was followed by treatment-free observation periods of at least 30 days in nine patients and of 22 days in one patient.

The following clinical observations and laboratory examinations were made: (1) Subjective symptoms: headache, dizziness, nausea and others; (2) Objective symptoms: pulse, respiration rates, blood pressure, body temperature, bleeding symptoms; (3) Hematological findings: platelet count, hematocrit, hemoglobin, erythrocyte and leucocyte counts, leucocyte differentiation and reticulocyte count; (4) Coagulation and fibrinolysis tests: PTT, APTT, fibrinogen, FDP, antithrombin III, bleeding time and Rumpel-Leede test; (5) Blood chemistry: bilirubin, GOT, GPT, LDH, alkaline phosphatase, Gamma-GT, amylase, total cholesterol, triglyceride, total serum protein, protein fraction, BUN, creatinine, uric acid, Na, K, Cl, glucose; (6) Serological tests: Serum IgA, IgG, IgM, complement factors C_3, C_4, hemolytic complement activity (CH_{50}), HBsAg, HBsAb, HBcAb, RA factor, direct Coombs test; (7) Urinanalysis.

The safety of the treatment was assessed by considering all side effects, complications and incidental symptoms.

The effectiveness was evaluated from the increment in platelet count, graded as: marked increase ($> 30 \times 10^4/\mu l$); moderate increase of $10–30 \times 10^4/\mu l$; slight increase ($2–10 \times 10^4/\mu l$) or no change ($< 2 \times 10^4/\mu l$).

On the basis of both safety and efficacy, the treatment was rated: (1) highly useful, (2) useful, (3) slightly useful, (4) useless, or (5) impossible to use.

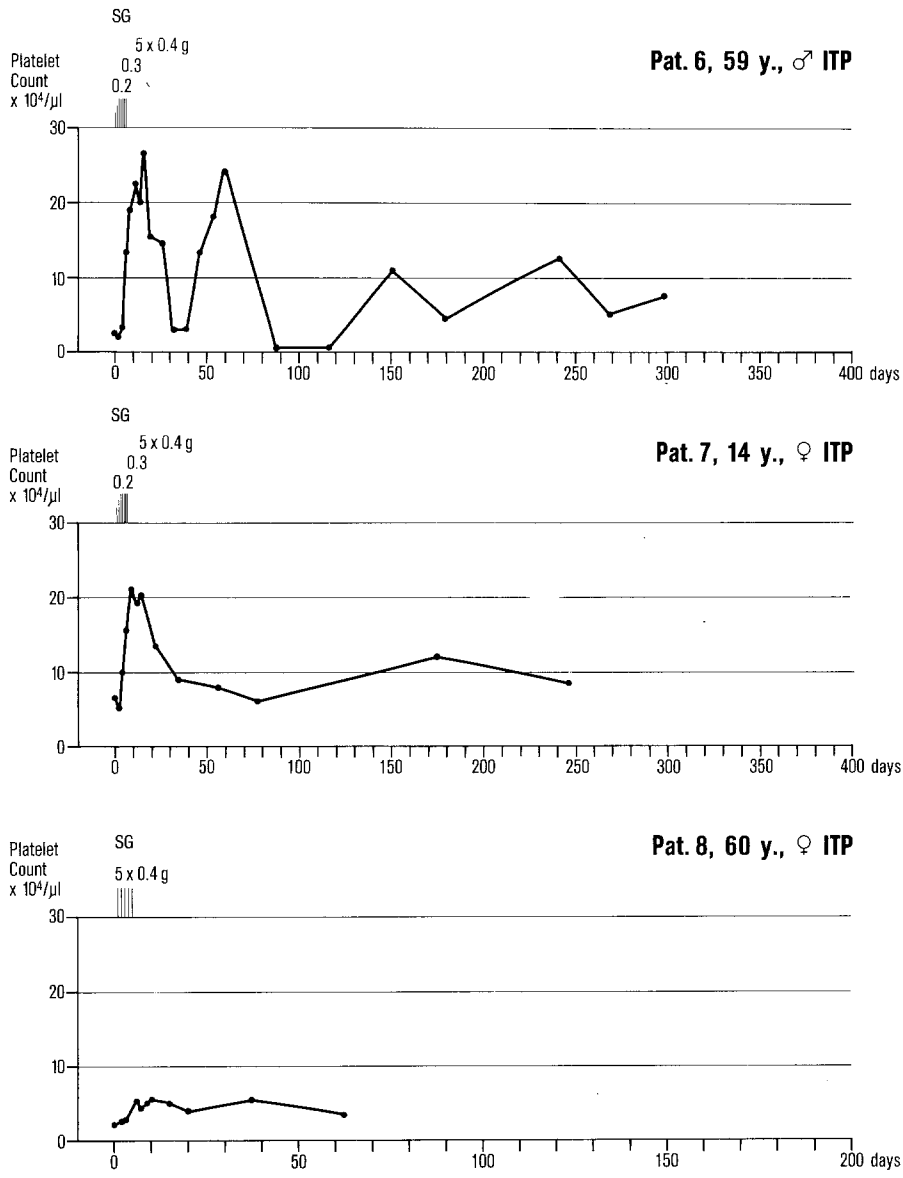

Fig. 2. Variation of platelet count after Sandoglobulin (SG) in patients 6–8 and 10 and after other Immunoglobulin preparations in patient 9. Figures denote g/kg body weight of SG except for patient 9

Results

In eight out of nine ITP patients slight to marked increases of platelet count were observed after SG-infusion, reaching in patient 9 a maximum value of $37.7 \times 10^4/\mu l$ from an initial count of $1 \times 10^4/\mu l$ (Figs. 1, 2). One ITP patient (pt. 4), however, did

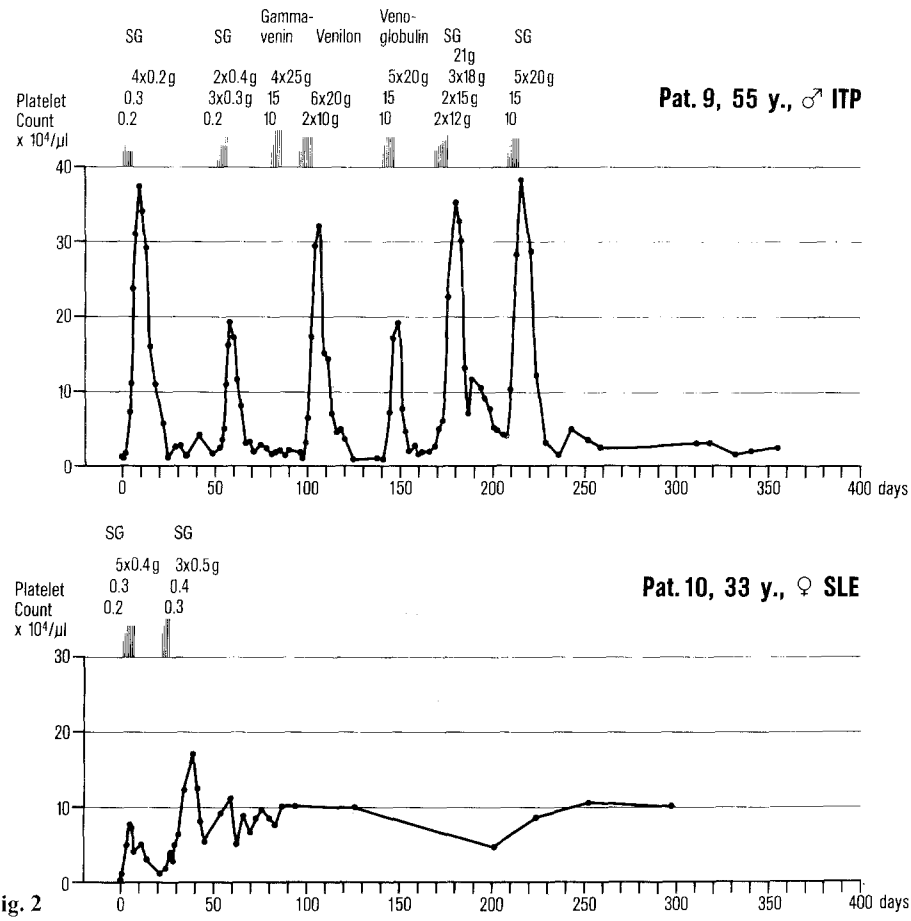

Fig. 2

not show any significant change of thrombocyte count. Patient 10, who had SLE simultaneously with thrombocytopenia, showed a slight increase after the first SG-course and a marked increase after the second course. The longest elapsed time to reach the maximum counts from the initiation of infusion was 5 days and the increased platelet counts returned to their initial values within 14–50 days, except for patients 7 and 5, who maintained an increased platelet number. During the observation time of 20–290 days (Figs. 1, 2) the platelet counts of five out of nine ITP-patients and of the SLE-patient remained above the pretreatment values. Serum IgG concentration elevation showed good correlation with the increases in platelet count.

The detailed clinical and laboratory examination data showed no severe side effects or complications. Patient 6 had a reversible and clinical asymptomatic increase in SGPT and SGOT after SG administration. Three patients had headache occurring at the end of infusions. All other clinical parameters and laboratory tests were unremarkable.

Patient 9 received various immunoglobulin preparations one after another at intervals and showed good response to infusion of SG, sulphonated IgG and plasmin-treated IgG, but no response to that of high doses of pepsin-treated IgG. Later on this patient was advised to undergo splenectomy as the effect of SG on platelet count could not be maintained indefinitely. After one course of SG-infusion splenectomy was performed without any complication. However, no particular increment in platelet count was observed after the operation and the patient required SG-infusion again.

Discussion

Chronic ITP in adulthood is supposed to have a relationship with immunological reactions [1, 2, 6, 7], especially autoimmune processes. The complexity of the pathogenesis of ITP offers different explanations and hypotheses for treatment policies.

The discovery of Imbach et al. [5] that high dose immunoglobulin therapy could elevate platelet count in children with ITP, and subsequent observations [8, 9], gave us some hints to investigate its influence in adult ITP patients, to compare several IgG preparations, to investigate indication in one ITP-patient, and the effectiveness in a SLE-patient with thrombocytopenia.

Our results are comparable to those of a study in adult chronic ITP-patients in Great Britain [10]. The administered doses seem to be safe and effective. The comparison of several IgG preparations in one patient showed the necessity of an intact ITP-molecule, the pepsin-treated F $(ab')_2$ preparation showing no effect. The mechanisms underlying the increase in platelet count appear obscure, although the disappearance of the spleen scintigraphic shadow before and after IgG-administration in one patient supports the hypothesis of a blockade of the RES [8]. Many factors such as possible correlation of immunoglobulin concentration with platelet increment and immunological effects on cellular [6, 7, 11] as well as humoral [12–17] mechanisms e.g. antiplatelet antibody [12, 13], particularly absorbed on the surface of the platelets [14–17] are under investigation in our laboratory.

In clinical practice the application of immunoglobulin evokes economical problems. It is our aim, therefore, to find the relevant indications and adequate doses of IgG i.v. in ITP-patients as well as other immune disorders.

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