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Harmful and beneficial antibodies in immune thrombocytopenic purpura

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SUMMARY

Two facts support the definition of idiopathic thrombocytopenic purpura (ITP) as an immune disorder. First, antibodies against platelets, which often appear after a viral infection, provoke the increased elimination of these cells. Viral disease may change the complex immune response of the host at different levels. In chronic ITP, the consequences of the dysregulated immune system are autoantibodies, primarily against platelet glycoprotein IIb/IIIa. Second, pooled immunoglobulins from healthy blood donors may influence the imbalanced immune response in ITP. The initial study dose of 5×0·4 g of intact 7S IgG/kg body weight can now be reduced to 2 × 0·4 g/kg body weight in the majority of patients. The possible mechanisms of action of intravenous immune globulin (IVIG) are reviewed and updated in this article. The combination of effects on the humoral and cellular immune responses using IVIG in concert with cytokines may open up new therapeutic possibilities.

Keywords immune thrombocytopenic purpura autoantibodies against glycoprotein IIb/IIIa IVIG

INTRODUCTION

In the classical study of Harrington & Minnich in 1951 [1], a transient decrease in platelet counts was demonstrated when serum from patients with idiopathic thrombocytopenic purpura (ITP) was given to individuals with normal platelet counts (Fig. 1a). Later, the active factor was found to be an immunoglobulin either in the plasma or on the platelets. On the other hand a rapid increase of platelet count was observed in patients with ITP when pooled IgG from blood donations from healthy individuals was administered [2] (Fig. 1b). These two contradictory observations provoked studies of the pathogenesis of ITP and other autoimmune disorders, and suggested the use of intravenous immune globulin (IVIG) in a broad range of other immune-related or autoimmune disorders. The pathogenesis of autoimmunity and the mechanisms of action of IVIG are still far from being clear. In this article we summarize some of the recent progress.

HARMFUL ANTIBODIES

Viral antibodies cause cytopenias

In ITP and other immunocytopenias, antibodies against platelets, leucocytes and/or erythrocytes provoke the increased destruction of these cells. The appearance of antibodies against blood cells is often associated with viral infections. For example after infection or vaccination with measles, mumps or rubella, antibodies against platelets, neutrophils and red cells with no antigen specificity have been noted to appear [3,4], and increased numbers of circulating, activated T cells have been observed [5]. In children with human immunodeficiency virus (HIV) infection after maternofetal transmission or blood transfusion-related transmission, thrombocytopenia has been estimated to occur in about 40% of cases [6]. Specific anti-platelet antibodies [7,8], as well as circulating [9] or platelet-bound immune complexes [10], have been demonstrated in such conditions. Megakaryocytes may contain HIV-related ribonucleic acid, which suggests a direct involvement of progenitor cells in the development of thrombocytopenia [11]. Neutropenia becomes more severe with progression of the HIV infection [12–14]. The production of anti-platelet and anti-neutrophil antibodies seems to be due primarily to B cell polyclonal activation by HIV [15]. Epstein–Barr viruses (EBV) stimulate B lymphocytes to enhanced production of antibodies which cross-react with normal tissue proteins, exhibiting configurations similar to those of the infectious agent [16]. This corresponds to molecular mimicry. Agranulocytosis due to EBV infection has been observed also in conjunction with bone marrow hypoplasia [17]. Cytomegalovirus (CMV) protein is similar to the human leucocyte antigen (HLA)-DR β chain protein, and shares a common epitope with it [18]. Thrombocytopenia has been observed in both congenital and acquired CMV infection. CMV infection is known to induce multiple autoantibodies [19], and human CMV can suppress haematopoiesis [20]. Human parvovirus (B19) inhibits haematopoietic colony formation *in vitro*. Thrombocytopenia, neutropenia and erythrocytopenia, as well as pancytopenia due to parvovirus infection, have been reported [21–25].

Viral disease may change the complex immune response of the host at different levels (Fig. 2). Antigen-presenting cells may be disturbed; T cells may be influenced by altered cytokine production and release, thus disturbing further activation of the network of the immune system; B cells may produce

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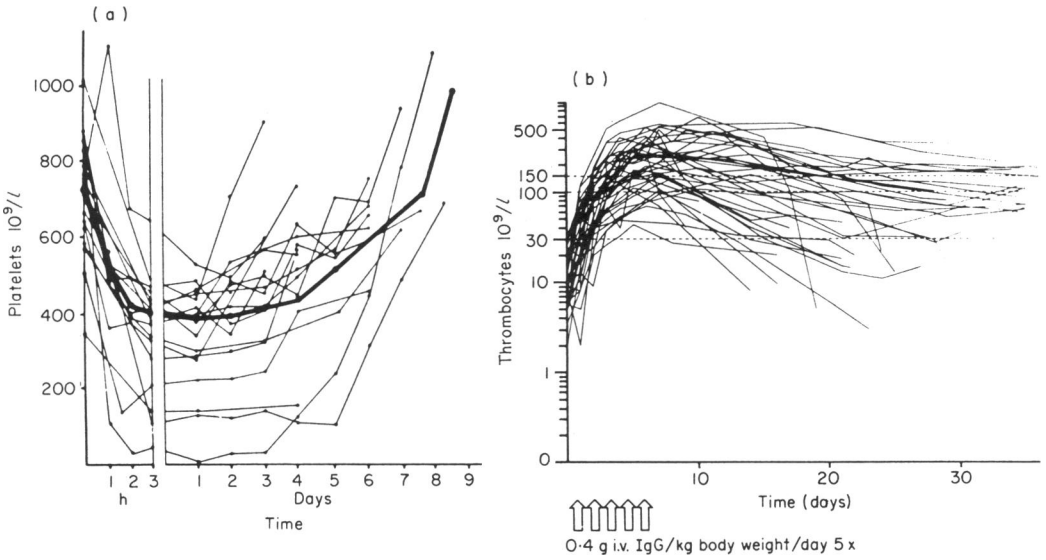

Fig. 1. (a) Platelet counts of volunteers after infusion of ITP plasma [1]. (b) Platelet counts of 42 children with previously treated ITP during and after IVIG therapy [31]. Fig. 1a is reproduced with permission from Mosby-Year Book Inc, and Fig 1b is reproduced with permission from Springer Verlag GmbH.

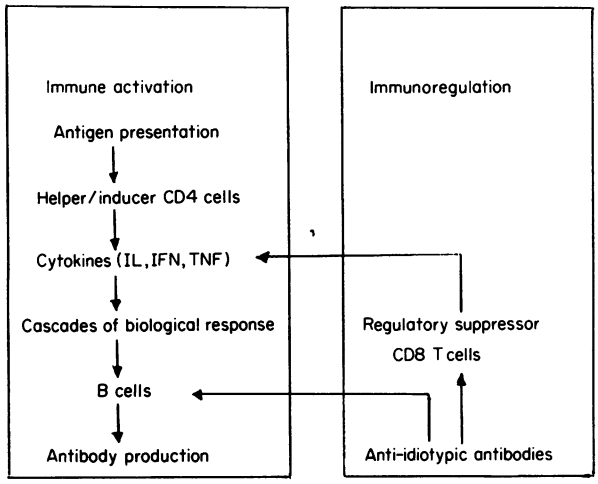

Fig. 2. Immune activation and regulation. IL, interleukins; IFN, interferons; TNF, tumour necrosis factors.

increased amounts of antibodies and, as one of the consequences, the feedback mechanism of the immune system may be dysregulated.

The autoimmune character of antibodies

In ITP antibodies are often directed against the glycoprotein IIb/IIIa complex on the platelets. The presence of antibodies against platelet glycoproteins was first suggested by the studies of van Leeuwen *et al.* [26], who reported that eluates from platelets sensitized with ITP plasma would bind to normal platelets, but only about 17% would bind to thrombasthenic platelets. Thrombasthenic platelets lack platelet glycoprotein IIb and glycoprotein IIIa, so the authors postulated that ITP plasma contained autoantibodies against these glycoproteins. Since then, several groups have confirmed this hypothesis by directly demonstrating the presence of glycoprotein-specific autoantibodies. In 1987 two new assays were described that are more sensitive: the immunobead assay [27] and the monoclonal antibody-specific immobilization of platelet antigen (MAIPA) assay [28]. Using the immunobead assay we evaluated pretreatment platelet and plasma samples from 67 children and 23 adults with chronic ITP for autoantibodies [29] (Table 1). At the time of sampling, 36 children had thrombocytopenia (mean duration 4·7 years, range 0·5–15 years) and 31 had normal platelet counts, although thrombocytopenia had been documented in the past (mean duration 2·9 years, range 0·5–9 years). Of the adult patients, 18 had thrombocytopenia and five had normal platelet counts. As shown in Table 1, platelet-associated autoantibodies were detected in 26 of 36 (72·2%) children with thrombocytopenia with chronic ITP, and in 15 of 31 (48·4%) children with a history of ITP but with normal platelet counts at the time of sampling. Of 23 adults with chronic ITP, 12 of 18 (66·7%) patients with thrombocytopenia were positive. A significant correlation was noted between the

Table 1. Anti-glycoprotein anti-platelet autoantibody (AAb) levels in chronic thrombocytopenic purpura

	Ongoing ITP*	Prior ITP†
Children ($n = 67$)		
AAb level ‡elevated	26/36	15/31
AAb level ‡negative	10/36	16/31
Adults ($n = 23$)		
AAb level ‡elevated	12/18	4/5
AAb level ‡negative	6/18	1/5

* Ongoing ITP, platelet count at the time of sampling $< 150 \times 10^9/l$.

† Prior ITP, history of platelet count $< 150 \times 10^9/l$ for at least 6 months but with normal counts, without therapy, at the end of sampling.

‡ AAb level, ratio of patient AAb value to that of the mean control value plus 3 s.d.

platelet-associated autoantibody level and the patient's age at the time of diagnosis. Children with high platelet-associated autoantibody levels were older, with a mean age of 12·4 years (range 8–17 years), compared with an average age of 7·1 years (range 1–16 years) in patients with moderate or negative autoantibody levels (< 5 times the mean control value ± 3 s.d. with a P value of 0·003).

These data suggest that there may be different forms of childhood ITP. Younger children with moderate autoantibody levels may have a greater chance of spontaneous remission or of compensated disease; the course of adolescents with high autoantibody levels seems similar to that of adults, in whom spontaneous remission or compensation is unusual. Children with chronic ITP in the past but normal platelet counts at the time of the study had elevated autoantibody levels, suggesting 'compensated' ITP, if their compensation were to be altered by factors that would decrease platelet production (for example a viral infection) or increase autoantibody production or platelet utilization. Furthermore the fetuses of such female patients may be at risk of neonatal thrombocytopenia.

The detection of autoantibodies against blood cells changed the definition of ITP to immune or autoimmune thrombocytopenia. As in autoimmune haemolytic anaemia and in autoimmune neutropenia, the rapid destruction of platelets is due to autoantibodies which bind via $F(ab')_2$ to the antigenic site, or to immune complexes which bind via Fc receptors on the platelets. These opsonized cells are rapidly removed by cells of the mononuclear phagocytic system, particularly in the spleen.

BENEFICIAL ANTIBODIES

When immune globulin preparations from healthy blood donors, containing innumerable different antibodies, are administered to an individual with an unbalanced immune response, the modes of action may be multiple. Each step of the above-mentioned immune response (Fig. 2) may be influenced, resulting in a more balanced immune response. What is today's treatment recommendation in ITP and what are the possible mechanisms of action of IVIG?

Treatment with IVIG

The key observation of the value of IVIG treatment in ITP was made in a 12-year-old boy who had life-threatening bleeding episodes, was unresponsive to conventional treatment and developed secondary hypogammaglobulinaemia [2]. Within the first 24 h after the initial dose of 0·4 g IVIG/kg body weight, his platelet count increased dramatically. After receiving 5 × 0·4 g IVIG/kg body weight, the boy's platelet count rose to normal levels. A pilot study [2], followed by controlled multicentre studies [30,31], confirmed the efficacy and low rate of mild side-effects of the possible new treatment. The main conclusions from these studies were: (1) the rapid increase of platelets in patients with acute bleeding symptoms; and (2) long-term improvement in some patients with chronic ITP without any further treatment.

Under study conditions the dosage of 5 × 0·4 g IVIG/kg body weight had to be used in all controlled trials. Soon it was realized that a lower dose of a total of 0·8 g IVIG/kg body weight had a similar beneficial effect in children with acute ITP. In a recent prospective, randomized, Canadian multicentre study of children with acute ITP and platelet counts below $20 \times 10^9/l$, comparing treatment with IVIG, oral corticosteroids and intravenous anti-Rh(D), the single dose of 0·8 g/kg body weight of IVIG demonstrated the fastest recovery to safe levels of platelets (V. S. Blanchette *et al.*, unpublished data). The fast recovery in children with the thrombocytopenic bleedings is important since the risk of intracranial haemorrhage is highest in the group with platelet counts below $20 \times 10^9/l$.

Today's treatment recommendations are summarized in Table 2. Three categories of treatment may be distinguished. First, in patients with severe bleeding or at risk of bleeding, i.e. before surgery, 0·8 g IVIG/kg body weight should be given initially. The subsequent treatment procedure depends upon the initial response (platelet increase within 72 h, duration of treatment effect). In life-threatening situations, the combination of IVIG, high-dose corticosteroids (8–12 mg/kg body weight/day), and platelet transfusion may be indicated. Second, in patients with long-term bleeding problems, and particularly in children, 0·4 g IVIG/kg body weight given at 2–8-week intervals is recommended, depending on haemorrhagic symptoms. Third, in patients with no or only occasional bleeding, no routine treatment is required. Some patients participating in special activities (i.e. sports) may need individual treatment.

IVIG in pregnant women with ITP

ITP and pregnancy is a risk for both the fetus and the newborn, since maternal antibodies cross the placenta. Platelets in the body are eliminated early, i.e. before and within the first few weeks after delivery. The risk of severe ITP ($< 50 \times 10^9/l$ platelets) is about 20% [32,33]. If a pregnant woman has previously delivered a baby with thrombocytopenia, the new infant is at high risk of bleeding. Fetal platelet counts should be determined by percutaneous umbilical vessel sampling or scalp vein sampling during delivery. If the platelet count is below $50 \times 10^9/l$, Caesarean section should be performed [34]. If the platelet count is higher than $50 \times 10^9/l$, the infant should be treated with IVIG prophylactically, since the platelet count often continues to decrease within the first few days after birth [35–37]. The recommended dosage of IVIG and the rate of response are the same as in children with acute ITP (Table 2).

Table 2. Treatment of ITP with IVIG

Initial treatment	
Day 1:	0·8 g IVIG/kg body weight
Day 3:	If platelet count is $> 30 \times 10^9/l$, no further treatment If platelet count is $< 30 \times 10^9/l$, repeat IVIG as on day 1 If platelet count is $< 10 \times 10^9/l$, bone marrow analysis for exclusion of production disorders of platelets, leukaemia, etc.
Emergency treatment (severe bleeding, presurgery)	
	1–2 × 1·0 g IVIG/kg body weight until platelet counts are at least $> 30 \times 10^9/l$ or there is no more bleeding. Eventually, combination with high-dose methylprednisolone (8–12 mg/kg body weight, intravenously or orally) and/or with platelet transfusion
Preventive treatment and treatment in chronic ITP (platelet count < 10–$30 \times 10^9/l$)	
	0·4–0·8 g IVIG/kg body weight, once

MECHANISM OF ACTION OF IVIG

IVIG may exert its beneficial effect by improving the clearance of infectious agents as a result of changes in Fc receptors (FcR) on phagocytes or by causing modulations of T and B lymphocytes associated with changes in release of mediators and changes in antibody production.

Clinically immediate and long-term effects of IVIG can be recognized. The immediate effect of IVIG may be due to modulation of FcR on phagocytes. In ITP, an association is observed between increase of platelet counts induced by IVIG and the prolonged survival of anti-Rh(D)-coated erythrocytes [38]. This association suggests that inhibition of FcR-mediated phagocytosis is responsible. Further evidence for an IVIG-induced reduction of FcR-mediated destruction of platelets by phagocytes was supplied by the experience with a monoclonal antibody directed against the FcR [39]. After infusion of this antibody, a patient with refractory ITP responded with a transient increase in platelet counts. In parallel, his neutrophil counts significantly decreased. Others have observed changes in leucocyte counts or in lymphocyte subpopulations that were inversely proportional to the platelet counts during IVIG treatment of some adults with ITP [40]. These observations suggest that not only the mononuclear phagocytes of the reticuloendothelial system but also other FcR-bearing cells are affected by IVIG infusion. The possibility that IVIG may modify complexes on the platelet surface, composed of viral products and antibodies directed against them, remains to be examined. Such complexes have been shown to be present also on the platelets of thrombocytopenic patients with acquired immune deficiency syndrome (AIDS) [41].

Modulation of immune responsiveness may be responsible for the long-term effects of IVIG. Reduction in autoantibody levels in patients with factor VIIIC inhibitors [42], in patients with myasthenia gravis [43], or in patients with any other autoimmune disorder accompanied by high antibody production [44], suggests the possibility of a B cell suppressive effect. Such a mechanism could be due to (1) the presence of anti-idiotype antibodies in IVIG; or (2) secondary changes in the immune response resulting from the establishment of a new humoral homeostasis after IVIG, which may down-regulate the patient's own autoimmune response. Another possible explanation may be that IVIG contains antibodies with the capacity specifically to block FcR [45]. Blocking by FcR, either by Fc portions of IgG or by anti-FcR antibodies, may have profound effects on lymphocyte functions, including down-regulation of autoantibody synthesis. A similar mechanism may be involved in patients with antibody-mediated pure red cell aplasia, where autoimmunity against haematopoietic precursor cells could be suppressed by IVIG [46]. This mechanism may also offer a tentative explanation for the effect of IVIG in patients with a decreased production of platelets in the bone marrow due to the presence of cytotoxic antibodies directed against megakaryocytes. Both types of interactions seem to play a key role in the immunomodulating effects of IVIG.

FUTURE PERSPECTIVES

The different possible mechanisms of action of IVIG were the rational basis for the use of IVIG in the treatment of patients with other immune-related disorders, where the humoral immune support showed more or less dramatic beneficial effects [47,48]. *In vivo* the humoral immune response is working in concert with the cellular immune response and vice versa. IVIG modulates the synthesis and release of cytokines by lymphocytes and monocytes [49,50]. Since recombinant cytokines for therapeutic use are available, the clinician may now attempt to optimize or maximize the immune response of patients by testing the combination of IVIG and cytokines. For illustration the following example of a preliminary observation is presented. A boy with acute lymphoblastic leukaemia of the preB lymphoid phenotype, in his third relapse and with increasing percentages of peripheral lymphoblasts despite chemotherapy, was treated sequentially with a combination of IVIG and cytokines (Fig. 3). The rationale for the administration of granulocyte colony-stimulating factor (G-CSF)/granulocyte–macrophage colony-stimulating factor (GM-CSF) was to stimulate the growth and differentiation of

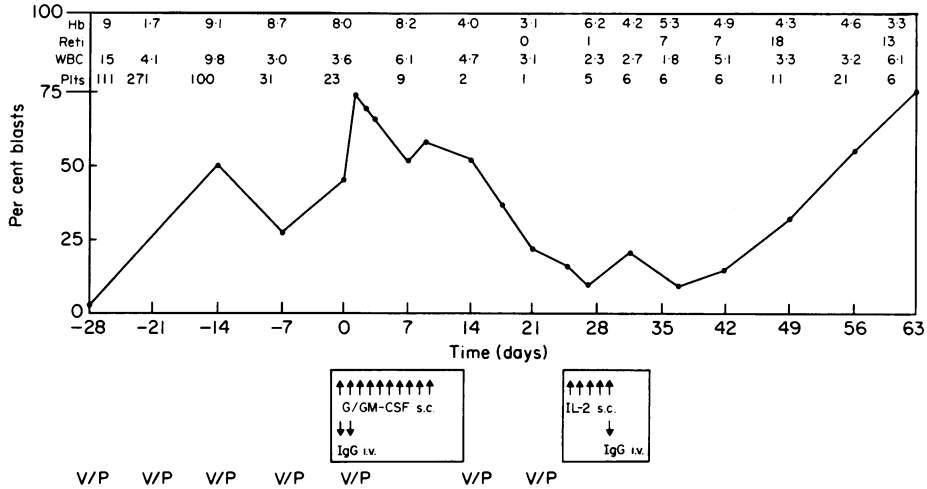

Fig. 3. Percentage of peripheral lymphoblasts before, during and after combined treatment with IVIG and cytokines in a 6-year-old boy with third haematological relapse of acute lymphoblastic leukaemia, unresponsive to conventional chemotherapy. Hb, haemoglobin; Reti, Reticulocytes; WBC, white blood cells; Plts, platelets; V/P, vincristine/prednisone.

neutrophils and monocytes and to activate the antigen-presenting cells. Two weeks later interleukin-2 (IL-2) was administered with the aim of stimulating regulatory T cells. As shown on the figure, the peripheral blast counts decreased dramatically within 4 weeks of the cellular and humoral immune support. After that treatment period the immediate increase of peripheral blasts underlined the transient effectiveness of the supported immune function against cancer cells. Investigation of the molecular mechanisms and regulation of the network of immunity by the influences of IVIG and cytokines may open up additional strategies for cancer treatment.

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