Paul Imbach
*Editor*

# Antibody Therapy

## Substitution – Immunomodulation – Monoclonal Immunotherapy

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*The path of antibodies therapy from substitution to immunomodulation to the development/use of monoclonal antibodies for patients with immune deficiencies, inflammatory, autoimmune and oncological diseases – based on the similarities of the immune pathogenesis, namely the loss of immune tolerance – is presented*

# Foreword

In 1735, Werlhof described a clinical syndrome of bleeding and purpura long before platelets were identified as the cellular component of blood that play an essential role in primary hemostasis. Werlhof's disease, as it became known, was later renamed idiopathic thrombocytopenic purpura, from which the acronym ITP originally derives. Little followed from these observations until the early 1900s, and we have just passed the centenary of the first successful treatment for the condition. In 1916, a medical student in Prague, Paul Kaznelson, proposed that, in an analogy with hemolytic anemia, essential thrombocytopenia, as it was also known, resulted from increased platelet destruction in the spleen. Kaznelson convinced his tutor to perform a splenectomy in a 36-year-old woman with a history consistent with our current definition of chronic ITP. The platelet count was $2 \times 10^9$/l prior to splenectomy and rose to $500 \times 10^9$/l within four weeks from surgery with complete resolution of the purpura. This confirmed the role of the spleen in the pathophysiology of ITP, and splenectomy has remained a mainstay of treatment ever since. The pathophysiology of ITP remained elusive for many decades. Although some intriguing observations by Dameshek and Miller in 1946 suggested reduced megakaryocyte function, the "increased platelet destruction, reduced production" debate appeared to have been settled by the classic Harrington-Hollingsworth experiments in 1951 that unequivocally demonstrated that ITP was characterized by reduced platelet survival due to a humoral factor that was soon identified as an antiplatelet antibody. In his historical review of ITP in 2002, Paul Imbach reported that Harrington et al. had also observed a child with purpura born to a mother with chronic ITP that resolved in the child 3 weeks after birth, although the mother still had ITP, indicating that a humoral antiplatelet factor had been passed from mother to child.

At the same time, the successful use of corticosteroids and adrenocorticotropic hormone (ACTH) in elevating the platelet count was described by Wintrobe (1951), and standard-dose prednisolone has been considered the initial treatment for newly diagnosed ITP since then. Immunosuppressive agents were introduced in the 1960s, when the autoimmune nature of ITP was clarified.

A milestone in the treatment of symptomatic ITP in children, however, was the introduction of intravenous immunoglobulin by Paul Imbach in 1981. The efficacy of this treatment was subsequently validated both in adults and in pregnancy by Adrian Newland in 1983. Abdulgabar Salama introduced anti-D treatment and the

concept of macrophage blockade in 1984. James Bussel and his group later expanded the knowledge about the modalities of treatment with anti-D in various settings.

With an increasing understanding of the underlying molecular biology and with advances in pharmacological technologies, targeted therapy became more attractive and has been investigated since the 1980s in many conditions. In ITP, the most consistent results with monoclonal antibody therapy have been obtained with rituximab, an anti-CD20 chimeric antibody inducing B-cell depletion. Roberto Stasi first reported the successful use of rituximab in adults with chronic ITP in 2001. This agent has become the standard (albeit unlicensed) treatment for patients with this condition in many countries, and its use has been extended to a variety of autoimmune conditions.

There is no doubt that in recent years, we have seen a major breakthrough in the treatment of chronic ITP, with the introduction of the thrombopoietin receptor agonists. The pioneering work of David Kuter with these agents has shown response rates unequalled by previous medical therapies. These agents are almost as efficacious in splenectomized patients as in the non-splenectomized ones, and recent studies have confirmed the efficacy and safety following long-term usage.

The second half of the twentieth century brought recognition on the autoimmune components of ITP, hence the need for a new standard nomenclature, which has been widely accepted. ITP currently stands for immune thrombocytopenia, a name that more appropriately reflects the low platelet count rather than purpura as the main feature of the disease and defines its underlying nature.

Advances in our knowledge of the disease have paralleled the burgeoning availability of new therapeutic agents, and we are now entering an era of treatment options based on pathophysiological principles. There is no doubt that the enormous expansion in our understanding of the condition and its treatment was stimulated by the observations of Paul Imbach in children with thrombocytopenia. A relatively rare disease with few treatment options, the disease suddenly became totem for clinical study and laboratory investigation and a marker for the possibilities in other autoimmune diseases. It was Imbach's realization that intravenous immunoglobulin was more than a replacement treatment but that it had a major impact on both immunological and phagocytic functions that had implications in a wide variety of conditions. This book systematically charts the history and the development of immunoglobulin and its association with ITP while highlighting how treatment and understanding of the latter has changed and how the former has developed into an important therapeutic option. Our forebears would be astounded at the progress over the last 50 years which is admirably described in these chapters.

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# Contents

# About the Editor

**Paul Imbach** is a highly respected pediatric oncologist-hematologist who has developed worldwide clinical research on the indications for intravenous immunoglobulin. Dr. Imbach graduated in Medicine in 1972. He went on to structure the Swiss Pediatric Oncology Group (SPOG) and in 1978 performed the first autologous stem cell transplantation in Switzerland. He discovered the immunomodulatory effects of human immunoglobulin G concentrate (IVIG) in childhood immune thrombocytopenia (as reported in *Lancet* in 1981). In 1990, Dr. Imbach began working at the University Children's Hospital Basel, where he started stem cell transplantation in children and was appointed Head of Pediatric Oncology-Hematology. He was subsequently elected as full professor and also as Dean of Education introducing a thorough curriculum reform at the medical faculty of the University of Basel. In parallel to his other activities, he co-founded the International Cooperative ITP Study (ICIS) group (www.itpbasel.ch), which now has more than 90 centers worldwide. He has served as president of medical societies and foundations, is a member of medical editorial boards, and has published over 350 peer-reviewed articles, textbook chapters as well as the textbook *Pediatric Oncology – A Comprehensive Guide* (3rd edition 2014) in German and English. In 2015 he was awarded the Guido Fanconi Prize, the highest award of the Swiss Society of Pediatrics.

# Introduction

The book starts with a narrative description including citations of the first clinical observation of immunoglobulin (IgG) administration in children with "idiopathic" thrombocytopenia. This highlights the importance of clinical observation, inquisitiveness and translational clinical research. This leads into a discussion of the fundamental discovery (Chap. 2).

Written in a practical fashion as manual, Chap. 3 describes some main indications of substitution by IgG in primary and secondary immune deficiencies and Chap. 4 summarizes many of the new immunomodulatory indications, some of which remain quite controversial.

Autoimmune disorders are characterized by complex heterogeneity of clinical presentation and pathophysiological abnormalities of the innate and adaptive immune system. Immunomodulatory IgG indications are rarely evidence based and in general are disorder oriented with specific individual indications. Based on the very large number of clinical and laboratory studies in the literature—over 40,000 peer-reviewed articles in Pubmed—a categorization of the indications is proposed in the manual of autoimmune disorders.

One specific IgG preparation is Anti-D, which is a targeted product specifically binding to the Fc receptors as its mechanism of action; in contrast the polyclonal IgG concentrate induces a broad spectrum of synergistic immune challenges to the imbalanced immune system in patients with autoimmune disorders.

Chapter 6 is dedicated to the general immunomodulatory effects of IgG followed by a chapter that covers classical drugs, IgG and monoclonal antibodies with exploration of their mechanisms of action. The combination of the different immunomodulators often results in a more effective clinical outcome in the individual patient. The first part concludes with two expert reviews of the current use of IgG in conjunction with other therapeutic options in both neurology and dermatology.

The second part of the book updates the basic knowledge of the IgG molecule starting with historical aspects of polyclonal IgG. Currently production and the regulations for a safe and effective IgG product are complex. Many such preparations are now available internationally, and these are listed highlighting their specific characteristics with a consideration of the future perspectives of IgG preparations.

Since 'idiopathic', now immune thrombocytopenia ITP was the key disorder of the first observation of immunomodulatory effects of IgG, the third part summarizes ITP as the model syndrome of autoimmune disorders. In the majority of children

with ITP the condition will resolve within weeks, months or very occasionally years. In adults the position is more complex with few spontaneously remitting and many developing chronicity. There has therefore been much interest in identifying prognostic factors, studying clinical outcomes and reviewing health-related quality of life issues in mild, moderate or severe disease. In order to standardize treatment approaches guidelines have been developed and regularly updated. There is increasing interest in secondary ITP and how it relates to the primary condition.

Newer aspects of platelet function are being recognized. Before 1980 the platelet was mainly thought to be responsible for coagulation, but now it is increasingly recognized as having an active role within the immune system (Chap. 17).

For many years the role of megakaryocytes has been suspected in the pathology of ITP, and the recognition of reduced platelet production led to the development of platelet stimulation by recombinant thrombopoietin and thrombopoietin receptor agonists, which is the focus of Chap. 18. For patients with severe, chronic ITP, e.g. with recurrent or at risk of life-threatening bleeding, thrombopoietin receptor agonists have become a major option with a low adverse event profile and increasingly have a place early in the treatment of refractory or relapsed disease. Chapter 18 summarizes the development and the characteristic of this long-term approach.

Nevertheless, in patients with acute, life-threatening bleeding immediate high dose IgG and/or corticosteroid administration and occasionally platelet transfusion remain the first choice.

The heterogeneity and immunological complexity of autoimmune diseases was the reason to start worldwide online registries of patients with ITP. The first endpoint of these registries is to distinguish subgroup of patients concerning demographics and follow up of this rare disease (for details see Chap. 19 and www.itpbasel.ch). There is also a large adult registry in the UK (www.ukitpregistry.com). Through recognition of subgroups of an autoimmune disease, evidence-based trials might become feasible.

We are now entering an exciting new phase of a "bridge" from antibody therapy of human origin progressing to monoclonal, engineered (or human adapted, e.g. CAR cell) treatment as an immunomodulatory approach to both autoimmune disorders and cancer. In a critical overview Chap. 20 explains the definitions, methods and adverse effects of monoclonal antibodies and presents an extensive list of those currently available monoclonal antibodies and their possible indications. One of the first antibodies introduced into clinical use, anti-CD-20, is described in Chap. 21. The anti-CD 20 antibody was initially developed as an adjunct in the treatment of Non-Hodgkin Lymphoma NHL, but its activity against immune competent B lymphocytes led to its exploration in many immunological and oncological disorders—based on the similarities of the immune pathogenesis, namely the loss of immune tolerance.

In summary the use of IgG, monoclonal antibodies and a variety of combinations with other immunomodulatory approaches has opened up the path from translation to more targeted biological, therapeutic approaches for patients with unresolved immune and malignant disease.

We thank all our contributing authors and the staff of Springer, especially Mrs. Meike Stoeck and Mrs. Dr. Isabelle Arnold, for their commitment to this extraordinary book.

Basel, Switzerland Paul Imbach

# 1 The Clinical Translation of Intravenous Immunoglobulin from Substitution to Immunomodulation

Paul Imbach

The subject of the book highlights 37 years of experiences following the first observation emphasizing the importance of the skill of critical medical observation, the development and production of a safe human blood extracts with minimal adverse effects, and research on how the administration of IgG intravenously or subcutaneously benefits patients with other autoimmune disorders and the potential mechanisms of action.

## 1.1 History of New Observations

**1980** Pediatric Hematology-Oncology, University Children's Hospital Berne, Switzerland: On January, during a ward visit PI (the abbreviation of names relates to the full names in the reference list) and his colleagues observed a minimal increase in platelet count after each intravenous immunoglobulin G (IVIG) substitution in a child with typical Wiskott-Aldrich syndrome who also had thrombocytopenia in addition to hypogammaglobulinemia. On the same ward, there was a 12-year-old boy (M) with severe, refractory immune thrombocytopenia ITP of 9 years' disease duration with many complications despite splenectomy and cytotoxic treatment. The latter treatments resulted in secondary hypogammaglobulinemia and recurrent infections. Discussion with visiting colleagues led to the decision to ask for permission from the medical director ER to administer IVIG, and for consent from the patient with ITP and his parents. The first dose of 0.4 g IVIG/kg body weight was administered on the next Monday. During the evening visit, the boy said: "I am feeling much better, and I am sure that my platelet count will be much better tomorrow." This was the reality: his platelet count increased remarkably from 2 to 21 × $10^9$/L. Now, PI discussed the observation with the chief immunologist SB treating adults with primary immunode-

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ficiency with IVIG at the cancer research institute, who recommended to empirically continue the daily administration of the same dose of IVIG. On Friday of that week and after 5 × 0.4 g IVIG/kg body weight, the boy's platelet count was higher than $150 \times 10^9$/L.

In the following PI asked for permission to administer the same IVIG treatment regimen to other patients with severe, chronic ITP with platelet counts of less than $30 \times 10^9$/L and without hypogammaglobulinemia and as a control for two children with aplastic anemia. The IVIG was provided by the Swiss Red Cross, who were the local producers of the product. At this time, gamma globulin was the former name of IVIG.

In this pilotstudy children with ITP consecutively responded to IVIG, but children with aplastic anemia did not. Following these observations, the first manuscript was produced with input of his consultant HpW (Imbach et al.; see some citations (in cursive letters) and the Fig. 1.1 from the very first article below):

***Summary***

*A new immunoglobulin (IgG) for intravenous use was given in high doses to 4 children with refractory idiopathic thrombocytopenic purpura (ITP) and 2 children with idiopathic aplastic anemia (IAA). Within 5-10 days after initiation of IgG therapy the platelets of the children with ITP rose to 300,000-650,000/mm3 and could be maintained at normal levels with one IgG infusion every 1-3 weeks. No response of platelet counts, was observed in the 2 patients with IAA… The IgG treatment was tolerated without complication by all patients.*

*The effect of intravenous IgG on the number of platelets is shown in Fig. 1. (see below). The platelets of all patients with ITP rose to a maximum between 300,000 and 650,000 within 5 to 10 days and returned to values between 100.000 and 300,000/mm 3 within the next 10 days.*

*The platelet count of patients with aplastic anemia was not influenced by the IgG therapy during the period of observation.*

*Discussion*

*We do not know how i.v. IgG administration influences the elimination of platelets. One could postulate that IgG acts primarily on the reticuloendothelial system and diminishes its platelet-eliminating effect. This hypothesis would also explain why the non-splenectomized child with chronic ITP (patient 3) required more frequent IgG infusions than the two splenectomized patients with chronic ITP in order to maintain adequate platelet levels. We also do not know whether infused lgG has a different effect on platelets of children with chronic versus acute ITP. It should be noted that the child with acute ITP resistant to prednisone, after a single 5-day course of IgG, remained in unmaintained remission for at least 6 weeks.*

*Despite the fact that IgG had no effect on the platelet counts of our 2 patients with aplastic anemia, further trials, particularly in patients with immune aplastic anemia may be rewarding.*

*Finally, since the intravenous IgG therapy described was well tolerated and had a striking effect on the platelet count of 4 children with chronic or acute ITP, the question arises whether the use of intravenous IgG should be considered for other autoimmune diseases as well. Obviously, the mechanism by which intravenous IgG exerts its effects should be known more precisely (end of citation).*

In parallel with the first publication, the investigators continued to treat a total of 13 children with acute (7 patients) and chronic (6 patients) ITP using the same treatment regimen. Because all children in this pilot study showed responses to IVIG, the statistician determined the consecutive response rate to be a new phenomenon.

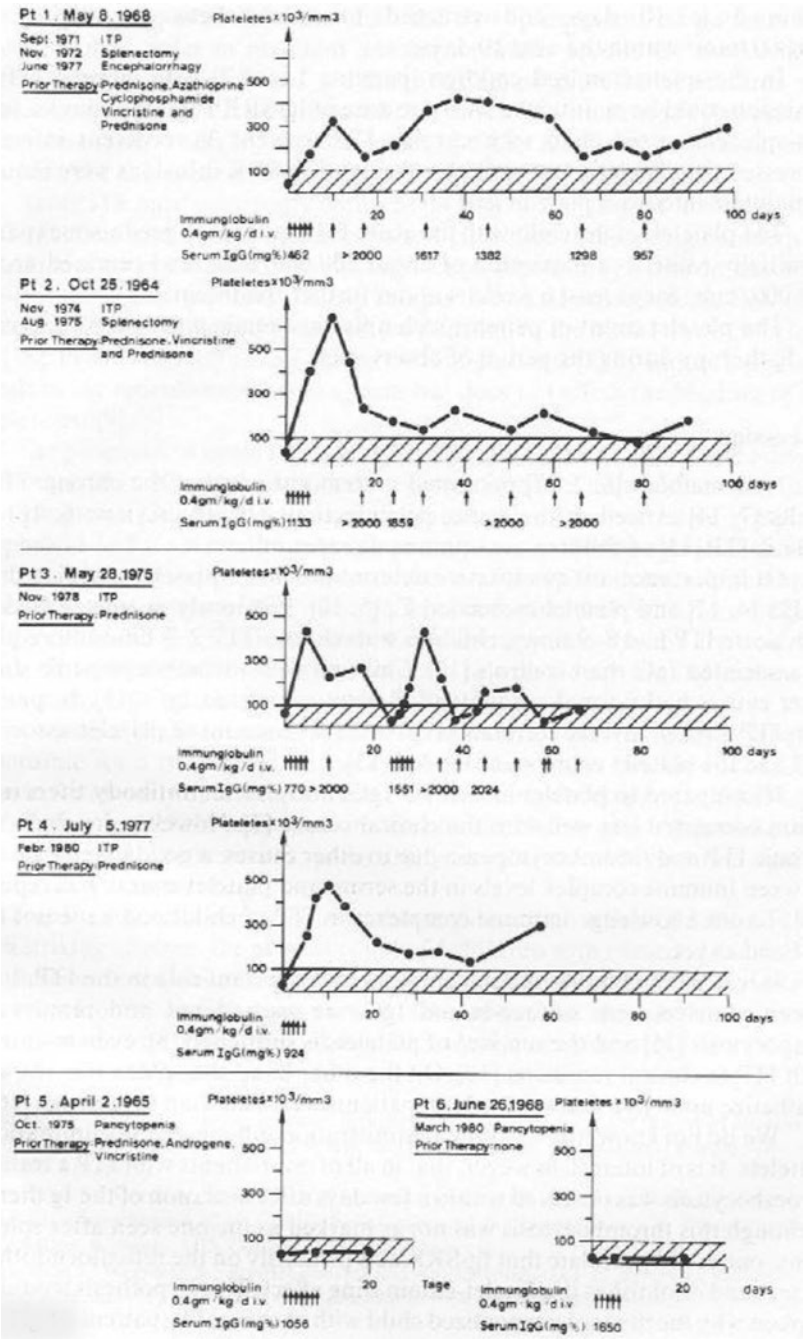


**Fig. 1.1** Effect of i.v. IgG: Patients 1–4 with refractory ITP: 0, 4 g i.v. IgG/kg body weight/day x 5 rose to 300–650 x 103/mm3 platelet counts within 5–10 days and could be maintained at normal levels with one dose of i.v. IgG every1–3 weeks. Patients 5 and 6 with idiopathic aplastic anemia: no reaction of platelet counts to the same doses of i.v. IgG

The group sent their manuscript to The Lancet. The editor in chief of The Lancet, made confirmation of the originality of the new observation, published it as a rapid communication. In the article and Fig. 1.2a and b (Imbach et al. 1981), it was stated (citations slightly modified):

***'Patients and Methods'***

*All patients first received, on 5 consecutive days, 0.4g IVIG/kg body-weight/day. IVIG is a polyvalent Ig concentrate obtained by modified alcohol cryoprecipitation, including mild acidification at pH4. The similarity of its in vivo biological half-life with that of normal serum IgG, and its intact Fc-receptor mechanisms reflect the structural and functional integrity of the 7S-IgG.*

***'Results'***

*No patient had adverse effects during and/or after immunotherapy.*

*IVIG induced a dramatic initial response in all patients (Figs. 1 and 2). In twelve of the thirteen children, the platelet count rose from pretreatment counts of <30x109/l platelets to a maximum of 150–600 x 109/l within 5-10 days of onset of treatment and returned to 80-400/ during the next ten days. In the thirteenth patient (patient 7), maximum counts were achieved after 10 days. Serum IgG levels rose to >2000mg/dl 10-20 days after onset of IVIG treatment (Figs. 1 and 2).*

***'Discussion'***

*The dramatic response to IVIG in patient 1 prompted us to give IVIG to other patients with chronic ITP and, later, to patients with acute ITP.*

*Although all of our patients showed a dramatic initial response to IVIG, the rates of increase and decrease and the maximum platelet counts differed between patients.*

*In view of the large IgG doses given, the mode of action of IVIG could be the overloading and blocking of the reticuloendothelial system by IgG catabolism. This explanation might account for the differences in the response patterns between splenectomized and non-splenectomized children with chronic ITP. Reaction with and inactivation of circulating antiplatelet factor or interference with platelet-bound IgG and/or C-3, could be responsible for immediate effects, and activation of T and suppression of B cells for late effects of IVIG. In one patient with acute ITP (not included in this study) 0.5 g of a pepsin-treated gammaglobulin (Fab')2/kg body-weight/day on 3 consecutive days did not influence the platelet count, whereas a single dose of 0,4 g of IVIG/kg body-weight raised counts from 1.7 to 6x109/l within 6 h and to 12.6x109/l within 18 h.*

*How IVIG works still needs to be investigated. The most effective and economic dose will also have to be determined.*

This article has been followed up by one for adults with ITP at the neighboring university (Fehr et al. 1982), by two other hemato-immunologists (Newland et al. 1983; Abe et al. 1983), and another colleague (Bussel and Hilgartner 1984). All confirmed the effects reported in the first publications. The observations led to much speculation on the many potential mechanisms of action and stimulated worldwide interest and study from clinical and laboratory investigators (see part III).

The nonprofit producer of IVIG was met with a high demand for the product and proposals for IVIG studies. Sandoz (later named Novartis), as a professional, worldwide distributor and coordinator of IVIG, took over that demand, while the local Red Cross expanded human-derived IVIG production, development, and research. The name changed from intravenous IgG to Sandoglobulin.

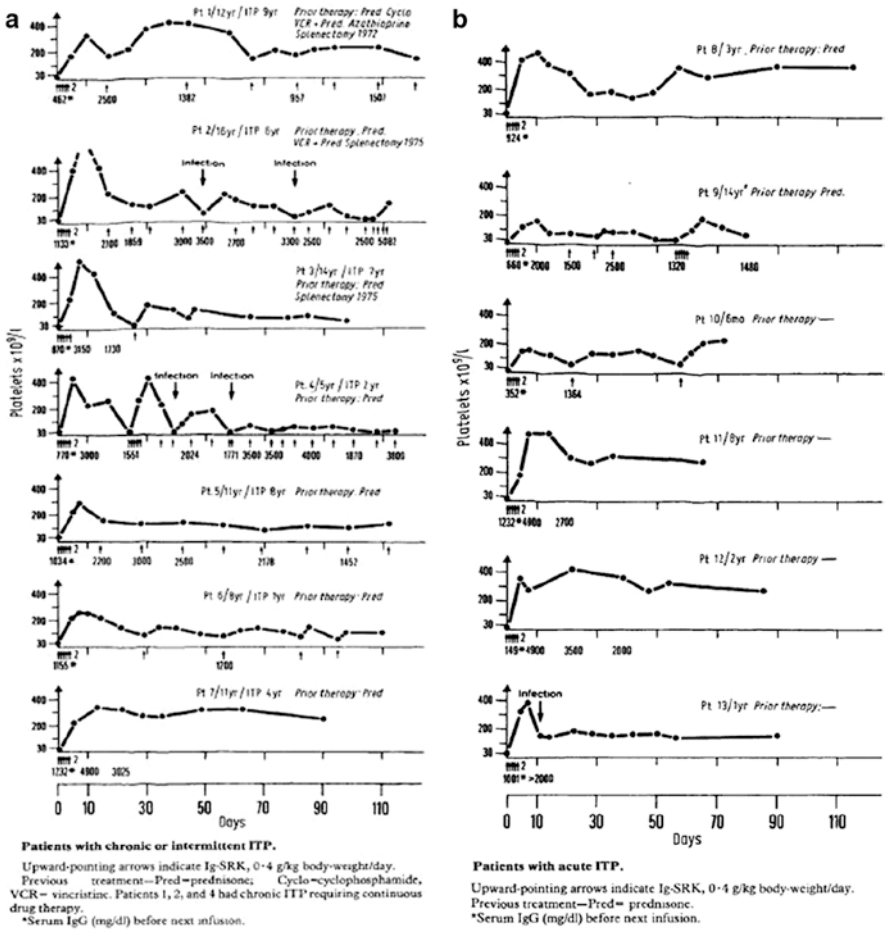


**Fig. 1.2** **(a)** Patients with chronic or intermittent ITP **(b)** Patient with acute ITP

**1981–1985** During a consultation at the University Children's Hospital Basel, the author met a well-known European expert of pediatric hematology EK, in Ulm, Germany, to whom he presented his data described above. This hematologist showed a great interest in the new, therapeutic possibility of IVIG. At that meeting, a proposal of an international cooperative study for administering IVIG to children with acute, newly diagnosed ITP was agreed (see below). This study was analyzed by BM and later published in "The Lancet" (Imbach et al. 1985). The article is entitled "An international cooperative, randomized study comparing IVIG with the classic corticosteroid treatment." Here are some citations:

***Summary***

*In a randomized, multicentre study treatment with intravenous IgG was compared to oral corticosteroids in 108 children with untreated acute immune thrombocytopenic purpura. IVIG was an efficient treatment with no severe adverse reactions reported. The effects of corticosteroids and IgG were identical for rapid responders, who accounted for 62% of all patients. In contrast, patients requiring more than initial treatment responded better if randomized to IgG. The serum levels increased two-fold after IgG. A significant rise in IgM levels was observed after both IgG and corticosteroids.*

***Introduction***

*In a pilot study, the same preparation at a comparable dose was found to have a similar effect in children with acute or chronic ITP and normal serum immunoglobulin levels. A randomized trial was set up to compare the efficacy in raising platelet count, potential side-effects, and the relapse rate and number of patients progressing to chronic ITP in previously untreated children with ITP given intravenous IgG or oral corticosteroids.*

***Patients and Methods***

*After informed consent had been obtained from the parents, the patients were randomized according to a computer-generated code to receive either IgG 0.4 g/kg body weight intravenously on 5 consecutive days or oral prednisone 60 mg/m2 daily for 21 days (initial treatment). If the platelet count did not rise within the first 7 days (non-responder) or fell below 30x109/l during the following 14 days (relapse), the patient was switched to the other treatment regimen.*

***Results***

*47 children randomized to IgG and 47 to corticosteroids could be evaluated. The two groups were well matched (see table below and Fig. 1.3)*

CHARACTERISTICS OF TWO STUDY GROUPS

| — | Corticosteroids | IgG |
|---|---|---|
| *n* | 47 | 47 |
| *M/F* | 22/25 | 23/24 |
| *Mean age* | 6 yr 3 mo | 6 yr 10 mo |
| *Mean initial platelat count ($\times 10^9$/1) (range)* | 9.8 (0.1–28) | 9.3 (0.2–28) |
| *Mean time from first symptom to therapy (days)* | 16.8 | 13.0 |
| *History** | | |
| Postinfectious | 33 | 38 |
| Insidious | 14 | 9 |

*No significant difference (p=0.337)

*36 of 47 (77%) patients randomized to corticosteroids and 39 of 47 (83%) randomized to IgG responded to the initial treatment (i.e., the platelet count rose to >100x109/l). The mean time to the peak count was 12 days with corticosteroids and 9 days with IgG.*

*Of the 47 patients randomized to corticosteroids, 27 needed initial treatment only. 12 of the 20 who required more than initial treatment crossed over to IgG, and in 5 patients the platelet count rose to >100x109/l. Of the 47 patients randomized to IgG, 31 received initial treatment only. 16 of 16 patients who required more than initial treatment were crossed over to corticosteroids and 6 responded.*

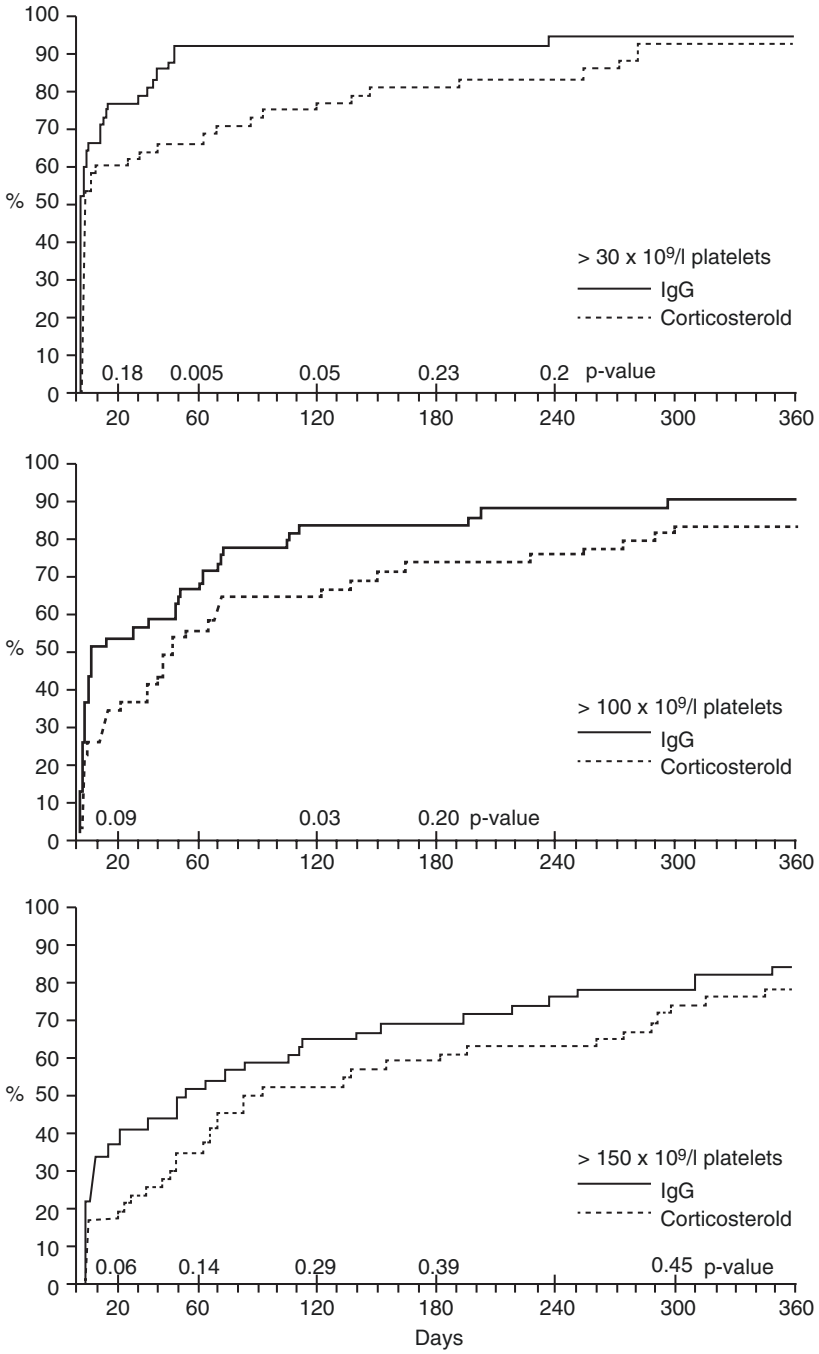


**Fig. 1.3** Percentage of patients with platelet count >30, >100, and >150 × $10^9$/1

*The percentage of patients with a platelet count of >30x109/l, >100x109/l, or >150x109/l at various times after starting therapy is shown for both treatment arms in Fig. 1. Significant differences were found at days 60 and 120.*

*The serum IgG concentration increased by a factor of two from an average pretreatment level of 12.5+/- 0.6 g/l to an average peak level of 25.9+/-0.9 g/l after five doses of IgG (fig. 3). Peak values were observed between days 4 and 7. During the next 4 weeks the serum IgG gradually returned to pretreatment levels.*

*In patients randomized to corticosteroids, the serum IgG concentration fell significantly over 5 weeks from average levels of 12.0+/-3.7 g/l to 7.8+/-2.8 g/l- After initiation of therapy, the difference in serum IgG concentration between the IgG and corticosteroid groups was significant.*

*The serum IgM level increased significantly in both groups, but the rise was greater (33%) in patients randomized to IgG (Fig. 1.4). 35 days after initiation of therapy the IgM concentration had returned to pretreatment values.*

*Adverse reactions were observed during or shortly after 14 of 474 (2.9%) IgG infusions; they consisted of headache (8 infusions) and/or fever (6), vomiting (3), and vertigo (3). These reactions were observed in 14 of 63 (22%) of the children treated with IgG. In 47 of 61 (77%) children who received corticosteroids a Cushing's syndrome developed initially or later with an increase in body weight of more than 10% (28 patients), acne (3), and other side effects (3).*

***Discussion***

*The best treatment for acute childhood ITP remains to be defined. The main aim is to prevent potentially fatal central nervous system haemorrhage, which occurs in less than 1% of all children with ITP admitted to hospital. 1 of the 108 children entered into our study died from CNS haemorrhage, despite receiving three doses of IgG. Thus, if there is no rise in platelets after one or two doses of IgG, the treatment does not prevent intracranial haemorrhage. At necropsy, this child had evidence of active disease.*

*In the prospective, randomized, double-blind, multicenter study Sartorius found that corticosteroids, compared with placebo, accelerated the initial rise of platelet count but did not significantly influence the further evolution of the disease.*

*Our results show that the intravenous administration of large quantities of structurally and functionally intact IgG is an efficient treatment for acute ITP, including a rapid rise in the platelet count in the majority of patients. Chronic ITP, defined as thrombocytopenia (platelet count < 150x109/l) for more than 6 months, developed in 43% of patients randomized to corticosteroids and 32% of those randomized to IgG. If the platelet count defining chronic ITP is reduced to <30x109/l, only 9 (19%) versus 4 (9%) patients met the criteria. Indeed, this latter group of patients with platelet counts below 30x109/l required treatment for longer.*

*The mechanisms by which corticosteroids and IgG act are unclear. Blockade of the reticuloendothelial system (e.g., by modulation of Fc receptor expression or by Fc receptor blockade), protection of platelet surface structure by monomeric IgG, or interference with free or platelet bound antigen and/or immune complexes have been postulated.*

*There was no correlation between platelet-associated IgG index and the platelet count of the serum IgG or IgM concentrations.*

*Despite IVIG treatment leading to significantly fewer side-effects and inducing a faster response in slow responders than corticosteroids for ITP patients, IgG has not yet become a generally accepted treatment for ITP, mainly because of the high costs.*

*In a preliminary study, we found that two infusions of 0.4 g IgG/kg body weight for rapid responders achieved a satisfactory response and Bussel et al have shown that hospital admission could be prevented by a single infusion of 1g IgG/kg body weight in about half of children with acute ITP.*

In the above-cited randomized study, it was not clear why IgM increased after both IVIG and corticosteroid treatment. Additionally, the results on

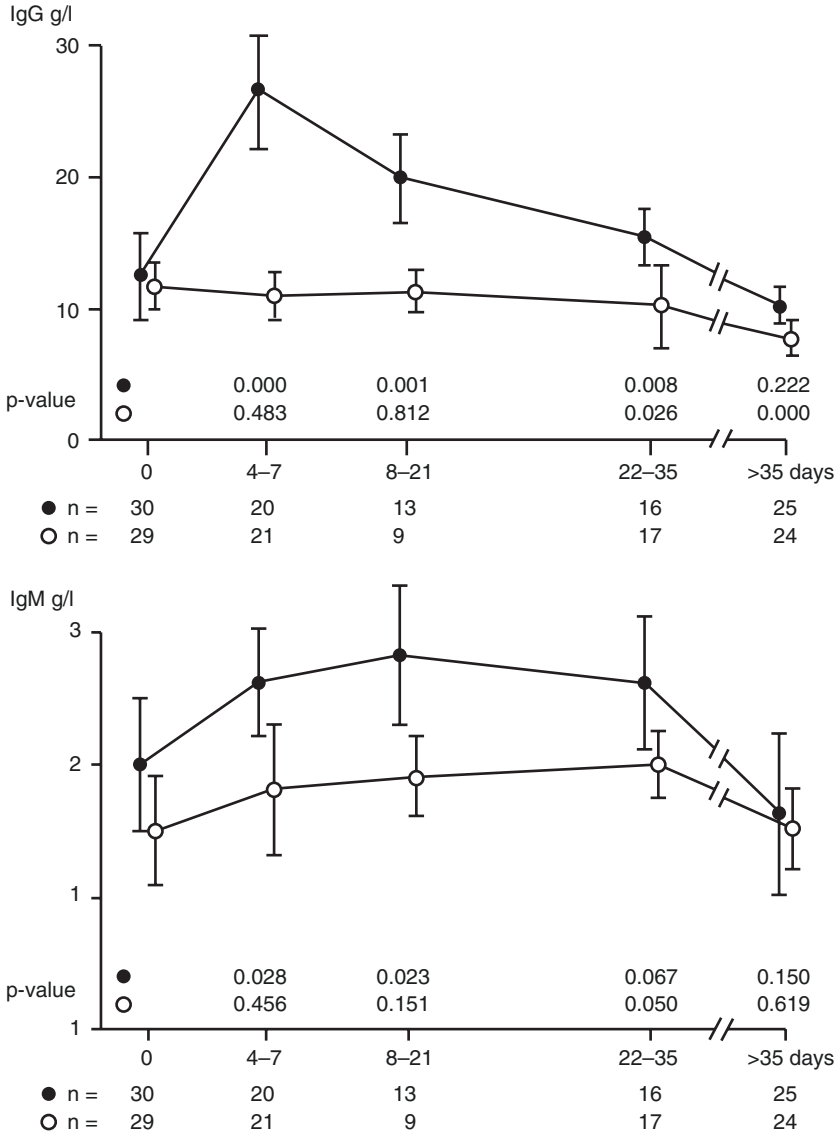


**Fig. 1.4** Serum IgG and IgM before, during, and after IgG (●) and corticosteroid (○) therapy. p-values indicate significance of differences between initial values and values at various times after initiation treatment

platelet-associated IgG (PAIgG, not cited above: see original article) are questionable; the sensitivity of the PAIgG test is high, but the specificity is low. Therefore, the author began to collect serum samples from children with ITP, and supplemented these with samples from adults provided by a colleague AN in the UK. With these samples, the author traveled to the Scripps Institute in La

Jolla, CA, where he could analyze PAIgG under supervision of RMcM (Imbach et al. 1991).

As mentioned above, after the pilot study was published in The Lancet in 1981, and after the start of the randomized study (Imbach et al. 1985), it was evident that "the high-dose IVIG treatment" had similar effects as 2 × 0.4 or 1 × 0.8 g IVIG/kg body weight in patients with ITP, doubling their serum IgG levels. A large, 4-arm, randomized, cooperative study was organized by Canadian colleagues, comparing 0.8 g IVIG/kg and 2 × 1 g IVIG/kg body weight with a higher dose (4 mg/kg body weight/day of corticosteroids during a short duration (4 days, then tapering) and anti-D IgG treatment, which confirmed the lower dose of IVIG treatment in ITP (Blanchette et al. 1994).

**1986** After completing the analysis of the randomized study in children cited above and the UK study in adults, the FDA in the USA and, later, the EMA in Europe accepted IVIG treatment as a new therapeutic for ITP. Thus, ITP became the first immunomodulary indication of IVIG as an autoimmune disorder.

**1990** PI transferred to the University Children's Hospital, Basel, where he continued his innonative work as head of pediatric oncology, hematology, and stem cell transplantation, earned the title of full professor and as dean of education performed a throughout curriculum reform at the medical faculty of the University of Basel. 1997 PI together with his colleague TK (Chap. 19) started the ongoing Intercontinental Cooperative ITP Study (ICIS) group which now has over 90 cooperating centers worldwide (www.itpbasel.ch).

## 1.2 The Translation of IVIG From ITP to Other Autoimmune Disorders

Since the immunopathophysiology of ITP is similar in many other autoimmune and chronic inflammatory disorders, IVIG became the subject of worldwide clinical and laboratory studies and of its mechanisms of action. PI as an independent consultant started to supported the clinical research and development group of the central laboratory of the Swiss Red Cross and Novartis. Many peer reviewed articles, symposia and presentations at congresses reflect the pros and contras the efficacies of IVIG which the present book critically update.

## 1.3 The Bridge of Polyclonal and Monoclonal Antibodies

Furthermore the bridge to the engineered, monoclonal antibodies is in the focus of this book by a basic knowledge, a updated list of target antibodies, their indication and adverse effects. PI would like that the monoclonal antibodies would be combined with the polyclonal IVIG in clinical trials with the endpoints of lower the side

effects and probably the increase of the efficacy. The high demand, the shortage of IVIG and the high costs of polyclonal and monoclonal antibodies might be the hindrance of such studies of antibodies combination.

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# Part I

# Update of Substitutive and Immunomodulatory Antibodies/ Drugs Indications

# From Immune Substitution to Immuno-modulation

2

Volker Wahn

## 2.1 History

The description of agammaglobulinemia by Bruton (1952) was a milestone in the history of medicine. For the first time it was shown that the absence of immunoglobulins was associated with recurrent mainly bacterial and viral infections and that the administration of Cohn fraction II subcutaneously (!) had the potential to reduce the number and severity of such infections. Today, the treatment of severe humoral immunodeficiencies consists in lifelong immunoglobulin replacement. Intramuscular administration has become obsolete because of injection site-related side effects but especially because only insufficient amounts of immunoglobulin can be administered.

Intravenous administration of Cohn fraction II probably as a consequence of complement activation by IgG aggregates offered no perspective. Thus, methods had to be developed to make products well tolerated by patients. After appropriate achievements, intravenous IgG (IVIG) replacement became the most widely used route of administration since the 1980s and allowed the administration of adequate immunoglobulin doses. IVIG treatment may be limited due to risk of anaphylactoid reactions and poor vein access in small children and because health-care personnel must, at least in Germany, directly supervise the infusions. As an alternative for iv IgG replacement, rapid administration (up to 50 mL/h) pumps for subcutaneous infusion (SCIG) are now generally accepted. SCIG was successively used for clinical trials in the Scandinavian countries since the early 1990s. Both intravenous and the subcutaneous administration achieve therapeutic IgG levels, and the clinical efficacy is comparable. One SCIG uses local administration of human recombinant hyaluronidase prior to IgG in order to increase the amount of IgG infused

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