

Where would immune thrombocytopenia be without intravenous gammaglobulin?

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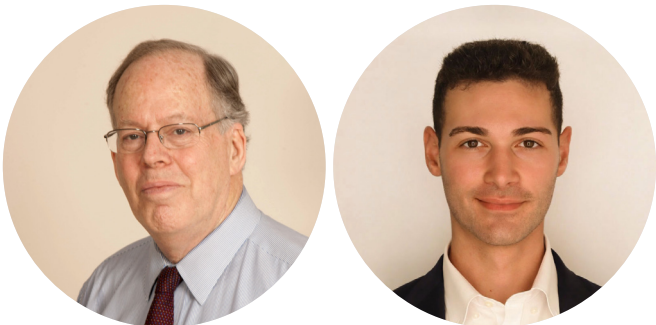
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TITLE	High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood.
AUTHORS	Imbach P, Barandun S, d’Apuzzo V, <i>et al.</i>
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The history of immune thrombocytopenia (ITP) before 1900 was somewhat unclear with no way to confirm the diagnosis, and a catalog of very uncertain, almost entirely unsuccessful treatments. Beyond discovery of the platelet, the modern history of ITP conventionally starts more than 100 years ago in 1916 with the first successful splenectomy.¹ This was actually borrowed from an Italian case in which splenectomy was performed and was successful in a patient with hemolytic anemia. Splenectomy was, thus, the first unequivocally successful treatment of ITP, although it rapidly became obvious that it would not work in everyone.² Then, in the 1950s, “steroids” were discovered and entered the ITP landscape, with many studies being performed. Immunosuppressive medications soon followed, especially vincristine and azathioprine, but the neurologic toxicity of the former (especially in adults with repeated infusions), and the slow onset of effect of the latter, greatly limited their use. Now fast forward to 1981.

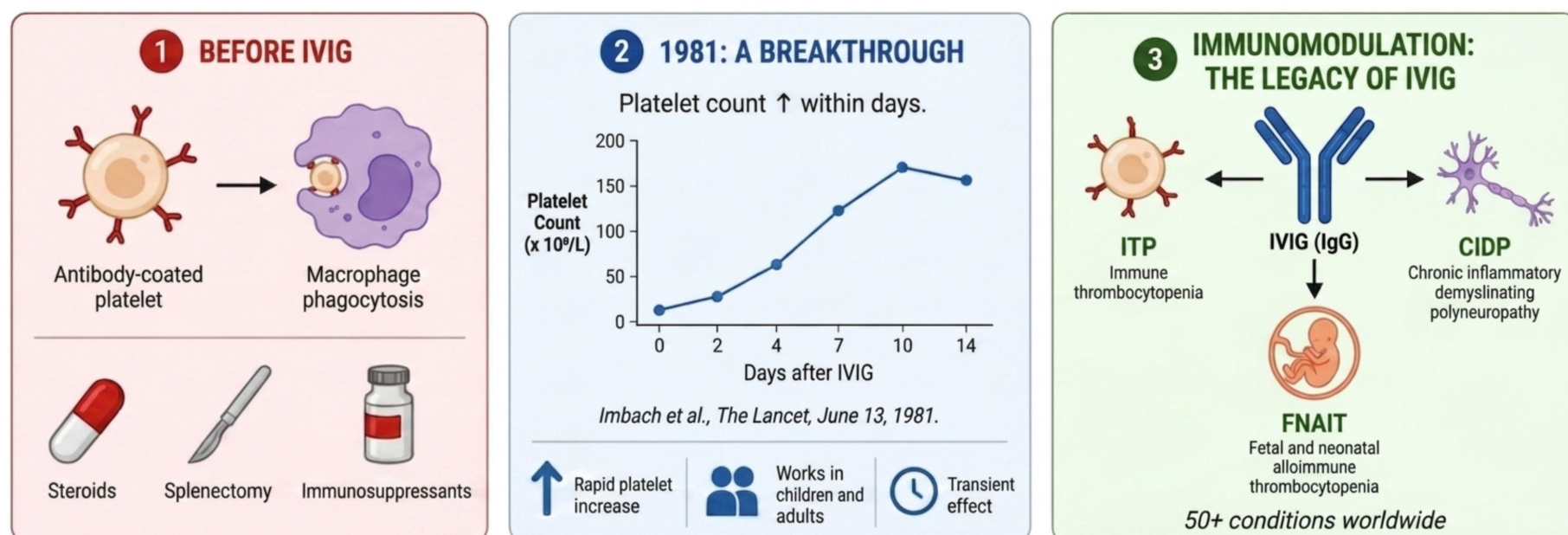
Immune thrombocytopenia in early 1981 was very different from today, in both its pathophysiology and treatment. A review by Robert McMillan showed that, in multiple studies, platelet antibodies (platelet associated IgG) were positive in approximately 90% of ITP patients, suggesting that “diagnostic testing” had arrived;² this, of course, did not last.^{3,4} Platelets were thought to be cleared by antibodies in minutes. Complex immunological considerations such as natural killer cells, dendritic cells, T-regulatory cells, and mesenchymal stem cells were not yet on anyone’s radar. Neither was the concept of decreased platelet production after the limited plasma infusion studies, aiming to provide thrombopoietin, were abandoned in the 1960s.⁵

As described, treatment was also not in a good place. For adults, steroids were the initial treatment and then management varied between 2 extremes. One was to proceed quickly to splenectomy if the platelet count fell below 50-100x10⁹/L with steroid taper. The other extreme was to use steroids “forever”, searching continually for the lowest dose that would maintain an “adequate” platelet count until lasting improvement occurred. A variation of the second approach was to attempt infusions of vincristine⁶ or to begin oral azathioprine,⁷ but compelling data to support their use regarding long-term sustained platelet counts were not available, whereas toxicity of the former was almost immediately evident. Thus, the big debate was: if you tapered the prednisone slowly enough (meaning usually over 2-3 months), would that prevent the need for splenectomy? If prednisone was started and a response was seen but relapse occurred while tapering, the critique would be: “tapering was too fast and prednisone should be tried again but tapered more slowly.” This was not an ideal situation given the toxicity of long-term steroid use, the risk of overwhelming post splenectomy sepsis,⁸ the (small) risk of surgery itself⁹ (which was not yet routinely laparoscopic), and the still-undiscovered risk of post-splenectomy thrombosis.¹⁰

In Pediatrics, there had been more than 5 completed or ongoing studies comparing prednisone to placebo (or no treatment) in newly diagnosed children with ITP.^{11,12} The platelet count increased more quickly in all the studies on the steroid arm. But long-term steroid use in children, as in adults, was clearly objectionable and undesirable.^{13,14} The goal in children was to await spontaneous improvement/

Where Would We Be Without IVIG For ITP?

Commentary on Paul Imbach's seminal 1981 study



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remission, which occurred in many but remained unpredictable, and could be years in the offing if it did ever occur.

Now that the stage was set, in June 13th, 1981, Paul Imbach and colleagues, including Silvio Barandun and Hans Peter Wagner, published a report of 13 children divided between acute and chronic ITP. The report demonstrated dramatic, albeit transient, platelet increases in both groups following IVIG 400 mg/kg daily for five days.¹⁵ This study in ITP followed the authors' observation of increased platelet counts in immune-deficient thrombocytopenic patients after they received their routinely administered IVIG. These results were so exciting and so different from what could be expected from any other treatment that many investigators, including the then junior Adrian Newland, Victor Blanchette, and myself, launched studies^{16–18} to see if we could replicate the results in children and use IVIG also to treat adults with ITP. Once the initial results were repeated in multiple studies, the next steps were wide-ranging: what was the right dose, how did IVIG compare to steroids, could this novel treatment be exploited to result in cures, and how did it work? The latter consideration, in particular, led to studies exploring in what other situations, especially other autoimmune conditions, IVIG would be useful.

Rather than retrace the now well-trodden path of the many, many studies of IVIG in ITP, it is important to highlight the broader, far-reaching impacts of this seminal study. First, the study of antibody-coated, chromium-labeled red cell clearance to learn more about the mechanism underlying treatment response^{19,20} opened the field of FcγR biology which had not previously been fully appreciated clinically. One example is the studies of Jeff Ravetch that uncovered the role of the inhibitory FcγRIIb.²¹ Another was the identification of anti-D treatment of ITP as another way to interrupt the destruction of antibody-coated platelets.²²

Still another was the augmentation of antibody-mediated phagocytosis by a polymorphism in FcγRIII. Second, the rapid onset of effect but transient response of IVIG in ITP heightened the appreciation of the need for a treatment of ITP that had a lasting effect, with or without ongoing treatment. Several studies showed that even repeated infusions of IVIG had a limited curative effect, highlighting the need for additional advances which now seemed more attainable.^{16,23} Third, the success of IVIG in ITP positioned ITP to be a testing ground for novel immunomodulating treatments as it became clear that serial platelet count measurements were more objective and much easier to obtain than, for example, serial joint scores or neurologic tests. Thus pharma, starting with anti-CD40 ligand, initiated early studies in ITP illustrating its utility across the study of a broad range of treatments.²⁴ Still today, IVIG is an effective, widely-used treatment in a wide number of conditions, not only in ITP and common variable immunodeficiency, but also chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)²⁵ and fetal and neonatal alloimmune thrombocytopenia (FNAIT)²⁶ (Figure 1).

Finally, Paul Imbach went on to further achievements. He created the Intercontinental Cooperative ITP Study Group (ICIS) which has provided large-scale data of ITP and several important studies.²⁷ Furthermore, he continues to hold international meetings focused on ITP at which experts gather to discuss the current state of affairs²⁸ and what is required for the future. Where would we be without this seminal study?

Disclosures

JBB reports consultancy for Rallybio, Janssen, Union Chimique Belge (UCB), and Argenx. JMH has no conflicts of interest to disclose.

Contributions

JBB conceived, wrote, and revised the manuscript. JH edited the manuscript, compiled the references, and created the figure.

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