Antibody Therapy

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Editor

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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 2×10^9/l prior to splenectomy and rose to 500×10^9/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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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