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Book Review

Antibody therapy: Substitution-immunomodulation -monoclonal immunotherapy, P. Imbach, editor (Springer International Publishing, Switzerland) 2018. 363 pages. Price: Not mentioned.

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This book provides a good exposition on the development of antibody-based therapy with a focus on clinical translation of intravenous immunoglobulin (IVIG) administration, beginning from immune substitution to immunomodulation in immune deficiencies and autoimmune, inflammatory and oncological diseases, highlighting the mechanism of action and transition from polyclonal to monoclonal antibody treatment. The book begins with a narrative description of 1981 Lancet publication of the editor Dr. Imbach that opened doors to IVIG usage from immune thrombocytopenic purpura (ITP) to autoimmune diseases and its subsequent commercial production to meet the ever-increasing demand.

The book has been divided into four sections for the sake of convenience in reading and better understanding. Part I starts with a chapter by Volker Wahn providing discussion on the history of intravenous IgG, fundamental aspects of its discovery, dosage required and clinical indications from ITP to other applications. Chapter 3 focuses on practical issues of management giving classical examples of major primary immunodeficiency diseases, secondary immunodeficiencies and other situations including haematopoietic stem cell transplantation and geriatrics. Similarly, one chapter is devoted to general characteristics and clinical care through immunomodulation of complex autoimmune and inflammatory diseases. For simplicity, the various diseases have been clinically categorized giving useful suggestions on disease-specific IVIG treatment.

Another polyclonal antibody namely anti-D used clinically for treating ITP and for preventing haemolytic disease of the foetus and newborn is presented in chapter 5. This chapter also describes Symphogen, a new therapeutic product as a possible replacement of anti-D. The monoclonal product, rozrolimupab recognizes multiple epitopes on the RhD antigen and has been found to be efficacious in ameliorating ITP. Chapter 6 provides an insight into the mechanism of action and immunomodulation by IVIG and discusses the possibility of replacing it with a monoclonal antibody for higher efficiency. It is ironical that although IVIG is used worldwide to treat a spectrum of autoimmune syndromes, its exact mechanism of action still remains elusive.

Chapter 7 is more general in nature covering therapeutic approaches to immunomodulation and the role of cytotoxic therapeutic agents and monoclonals. Two other chapters independently describe the current status on the use of IVIG in neurological and skin disorders, basing arguments on case-control studies and underlying pathophysiology of the disease. The authors caution on the indiscriminate use of IVIG for patients who may not need it anymore and suggest the need for biomarker discovery for clinical management.

The second part of the book describes the basics of IgG concentrates starting with the historical aspects of IgG preparation, adverse reactions of therapy, possible pathogen transmission to defining basics of immunoglobulins as effector molecules and drugs. Since IgG is the most abundant immunoglobulin isotype in human plasma that can bind with high degree of affinity and specificity to a remarkably large variety of antigens, chapter 11 is devoted to describing its structure-function relationship, four known subclasses, high titre immunoglobulin preparation and antibody repertoires in therapeutic products.

Most immunoglobulin preparations used today contain pooled human IgG prepared from plasma of healthy donors. The challenge is to prepare high titre

affordable polyclonal human IgG or monoclonal immunoglobulins for immunotherapy of infectious diseases and for passive prophylactic immunization. One good example of a monoclonal antibody in clinical use is bezlotoxumab for the treatment of severe *Clostridium difficile* infection. Chapter 12 highlights the essential requirements and international recommendations for the safe and efficacious production of polyclonal IgG concentrates that are universally well tolerated and are safe from transmission of known blood-borne viruses or the emerging and re-emerging zoonotic viruses. The importance of following assured quality assurance procedures through good manufacturing practice, good laboratory practice, pharmacovigilance and stability/tolerability of the final product has all been highlighted.

Most international products are FDA (U.S. Food & Drug Administration) and/or EMA (European Medicines Agency) approved. Chapter 13 gives a complete list of the available IgG concentrates, manufactured by various techniques and those available for intravenous and subcutaneous application. The list also includes products that are widely used and manufactured in different countries including those by companies in India.

The third part of the book is devoted entirely to ITP, not only because it was the first disorder in which the immunomodulatory effect of IVIG was described, but also because it eventually emerged as the model syndrome of autoimmune diseases. To that extent, chapter 14 provides current updates on ITP including management and clinical guidelines. The focus must be on assessment tools to determine the clinical status of patients with immune ITP and improve their health-related quality of life (HRQOL) through effective intervention. Authors highlight the importance of assessing the HRQOL and this might vary among various populations and countries, based on several factors. Since ITP is an acquired autoimmune disorder characterized by increased platelet destruction and decreased platelet production, the natural history in children varies from that in adults.

Currently, an important area of research is the discovery of biomarker predictors of chronic ITP. However, the current predictors are all based on demographic features and are hence not adequate in identifying patients who might develop clinically significant chronic disease. Genetic approaches are much needed for the discovery of novel biomarkers that can reliably predict the disease course in ITP.

The chapter on platelets describing their immune functions and MHC class I signalling is informative. Similarly, there is a comprehensive description on thrombopoietin receptor agonists, their clinical use and pharmacokinetics including associated risks and adverse effects in patients receiving therapy (chapter 18). Further, the activities of Intercontinental Co-operative ITIP Study Group (ICIS) including planning, and assessment of projects with international registries have been well summarized in chapter 19.

Part IV of the book takes an open view on the need for a shift from polyclonal to monoclonal antibody treatment. Chapter 20 gives an updated list of FDA-approved engineered therapeutic monoclonal antibodies as immunomodulators and anti-cancer agents, highlighting basic information and indications for adverse effects. The moot question is how does one increase the efficacy of these products with minimized side effects? It is equally important to address the issue of high demand, the shortage of potent IVIG and the high cost of polyclonal and monoclonal antibodies making their use restricted in resource-limited countries. The chapter covers description on production technology, factors influencing pharmacokinetics and therapeutic drug monitoring.

Clearly, the antibody-based immunotherapy has moved from the previously used polyclonal IgG plasma-derived mixtures to the more specifically engineered monoclonal antibodies. The technology has advanced to a stage to produce humanized antibodies for more effective and targeted therapy. The need is to design randomized clinical trials for safety and efficacy before putting them into regular use. The authors express caution on the use of such biologicals and biosimilars because of their high cost and possible severe adverse effects. The last chapter in the book is devoted to the use of rituximab in a host of autoimmune diseases, common variable immunodeficiencies, connective tissue diseases and others. This being an anti-CD20 monoclonal antibody induces rapid and profound depletion of B-cells, but not of plasma cells. The latter also need to be eliminated in organ transplant situations to avoid antibody-mediated rejection.

All in all, this is an exhaustive book describing from fundamentals to translation aspects of

immunoglobulin-based therapy in a host of autoimmune and malignant diseases, providing a compendium of FDA-approved products and their targets. The book fulfils the unmet need of clinicians and scientists, and its easy presentation style makes it a must read.

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