Focused themed issue on immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder mediated by anti-platelet autoantibodies and antigen-specific T cells (1,2). These immune effectors either destroy platelets peripherally in the spleen and/or impair platelet production in the bone marrow. The most recent pathophysiologic studies have shown that abnormal T cell responses, particularly, defective T regulatory cell (Treg) activity are central to the autoimmune pathogenesis of ITP and various therapeutics can restore these responses. Just in the last 2 years, for example, there is a significant literature on ITP pathophysiology and it points to the concept that the disease is initiated by flawed self-tolerance mechanisms (1). It appears that understanding how to specifically modulate T cells in patients with ITP will undoubtedly lead to effective antigen-specific therapeutics. This issue of AOB will be dedicated to ITP with a series of manuscripts written by leading experts in the field of ITP management and treatment. It now appears that a great deal of new treatments are available for the disease, and we now have a better understanding of how these new treatments may increase platelet counts in ITP.

In the first chapter, Branch (3) and colleagues re-visit what is known about the efficacy and mechanism of action of intravenous immunoglobulin (IVIg) treatment for ITP in adults. IVIg has been used for almost 40 years as a therapeutic for the treatment of ITP and was originally found to be an efficacious treatment for pediatric ITP and later for adults suffering from the disorder. The chapter delves into the success of IVIg treatment over the years and highlights its use with other therapeutics. It points out that despite its many years of use, the mechanism of action of IVIg in ITP still remains controversial with many experimentally-supported theories as to its mechanism of action. Even so, the authors suggest that IVIg will likely continue to be a first-line therapy for adult ITP, particularly when patients suffer from bleeding symptoms.

In the second chapter Schmidt (4) and colleagues discuss IVIg usage in pediatric patients with ITP. In childhood ITP, morbidity is significant due to the risk of bleeding and there is a reduced health-related quality of life (HRQoL). The authors suggest that IVIg treatment accelerates the remission of thrombocytopenia in newly diagnosed ITP and reduces bleeding symptoms, but there are disadvantages such as side effects and costs. They discuss their recent randomized controlled study (TIKI) that showed that IVIg does not affect the development of chronic ITP. It appears that approximately 60% of children with newly diagnosed ITP have a sustained response to IVIg and this response is associated with long-term remission. They then move into recent molecular and clinical data, which shows that treatment responders can be identified before IVIg administration and this is associated with a transient, self-limiting ITP disease course. They conclude by suggesting that the development of clinical and molecular prediction scores could allow for individualized treatment decisions and to design studies aimed at identifying children who benefit from adjunctive or alternative treatments.

Pediatric ITP continues as a focus of the third chapter where Kim (5) and colleagues focus on further treatments of childhood ITP. Many children have only mild bleeding tendencies and most will experience spontaneous disease resolution, however, this is not possible to predict. The authors focus in on the initial management of pediatric ITP which pays attention to careful screening measures to rule out secondary ITP followed by careful observation. When treatment is required, first line therapies are relatively standardized and aim to rapidly diminish bleeding risk, however, when ITP becomes chronic in nature, there is much less existing data on the optimal sequence of treatment choices. The authors suggest that pediatric ITP management continues to evolve and that further research will continue to expand our understanding of the molecular underpinnings of ITP.

Next, Poston (6) and colleagues discuss ITP associated with pregnancy and the unique challenges that ITP has in the peripartum setting. The diagnosis of ITP is similar to the nonpregnant patient except that pregnancy related causes of thrombocytopenia must be considered. The authors discuss how the management of ITP changes over the course of pregnancy and close monitoring is critical as delivery approaches when the recommended platelet count should be above 50×10^9/L for a vaginal delivery. In addition, if an epidural is required, the platelet count should be even higher (above 70×10^9/L). They then go on to discuss first-line therapies such as glucocorticoids or IVIG and point out that many second line therapies may be safe in pregnancy. On the other hand, contraindicated therapies include Syk inhibitors, vinca alkaloids, mycophenolate mofetil, cyclophosphamide and danazol, but a limited number of case series report safe administration of the thrombopoietin receptor agonists (TPO-RAs) without adverse fetal outcomes. They conclude that ITP is not a contraindication for pregnancy where women with a history of ITP should not be discouraged from becoming pregnant since they can be safely managed.

In the next chapter Newland (7) and colleagues discuss the role of neonatal Fc receptor (FcRn) inhibitors in the treatment of ITP. FcRn is a critical regulator in the homeostasis of IgG and albumin protecting them from degradation. FcRn-mediated extension of the half-life for IgG can prolong the serum half-life of IgG autoantibodies therefore promoting autoimmune disease and chronicity. By targeted reduction of IgGs through FcRn blockade, it prevents or reduces the pathogenic actions of anti-platelet autoantibodies. The authors discuss the role of FcRn as the central regulator of IgG homeostasis, the therapeutic approaches involving IgG reduction, and the clinical trial results of two FcRn antagonists currently investigated in patients with ITP, efgartigimod and rozanolixizumab.

Dr. Kuter (8) then focuses on the treatment of ITP with thrombopoietin receptor agonists (TPO-RA). He provides a personal overview of the diagnosis and treatment of ITP with a focus on the mechanism of action of TPO-RA and their place in the treatment algorithm of ITP and also, unique aspects of their clinical use. The three TPO-RA's, romiplostim, eltrombopag, and avatrombopag have markedly altered the treatment of ITP. Response rates of approximately 90% are commonly reached and these responses can be maintained with continued therapy. Recent data also shows that TPO-RA's are very effective in early ITP and the current guidelines recommend their use as early as 3 months into the disease course. In addition, the author points out that TPO-RA treatment does not need to be continued forever; about a third of patients in the first year and about another third after two years move to remission. Whether TPO-RA affects ITP pathophysiology and directly causes remission, however, still remains unclear.

In the next chapter, Hanif (9) and colleagues go on to present a systematic review of the recent literature on clinical trials pertaining to the primary and secondary management of primary ITP with a focus on novel agents. They discuss very recent (within 2 years) literature pertaining to articles discussing therapies other than the TPO-RAs or pediatric ITP treatments. They have collated evidence on corticosteroids and IVIG which remain the mainstay of first line management. With respect to second line treatments, in which rituximab and splenectomy were the prominent players, they discuss these and the new therapeutics including the Syk inhibitors, FcRn agonists, MMF and daratumumab.

Finally, we get a unique patient perspective on dealing with ITP. Kruse (10) and colleagues lead us through how patients with ITP face a complex set of challenges. The burden of living with ITP impacts the overall HRQoL of patients and their families. The authors review the patients' perspective on unmet needs, and the physical and emotional burden of disease in an attempt to highlight areas where healthcare providers can enhance their current approach to managing the patient with ITP. They emphasize that patients want their voices heard and their experiences with ITP acknowledged beyond simply treating the platelet count. They point out that aside from the constant risk of serious bleeding, patients also experience both physical and emotional consequences living with ITP and suggest that further studies are needed to clarify the nature and source of pain, anxiety, depression, and fatigue reported in both adults and pediatric patients with the ITP.

In summary, this theme issue on ITP is a current and comprehensive treatise of the treatments that have evolved over the years and will leave the reader with a new appreciation of the clinical management of the disorder. It was designed to touch on the major aspects of new treatments and unique situations of ITP e.g., in pregnancy. We believe that the reader will benefit from this comprehensive issue.

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