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What do we learn from immunomodulation in patients with immune thrombocytopenia?

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ABSTRACT

Current therapeutic strategies for autoimmune diseases primarily rely on immunosuppression, but global immune suppression results in an increased risk for severe infection and malignancy. In contrast, immuomodulation is another therapeutic approach employing intrinsic or environmental regulators that exert modulatory effects by intervening multiple checkpoints of the immune system, leading to correction of dysregulated immune responses. We have learned that immunomodulation by intravenous immunoglobulin is highly efficacious and safe in patients with immune thrombocytopenia (ITP), an autoimmune disease mediated by IgG antiplatelet autoantibodies. Recently, another types of immunomodulatory treatment are also effective for ITP. These include eradication of *Helicobacter pylori* and thrombopoietic agents, such as thrombopoietin receptor agonists. These treatment modalities are shown to exert immunomodulatory action by suppressing multiple checkpoints of the pathogenic loop of ITP, although only certain subsets of the patients show robust responses. Understanding mechanisms underlying immunomodulation is highly useful in clarifying pathogenesis of immune-mediated diseases and developing novel therapeutic approaches.

Current therapeutic strategies for immune-mediated diseases, including autoimmune, inflammatory, and allergic diseases, primarily rely on immunosuppression, which involves corticosteroids, immunosuppressants, and biologics targeting a variety of immune mediators. These treatment modalities are effective in general, and many patients are able to achieve clinical remission. However, global immune suppression results in an increased risk for severe side effects, including infection and malignancy. In addition, long-term use of corticosteroids is associated with a variety of comorbidities, such as cardiovascular events and osteoporosis, leading to shortened lifetime and impaired activity of daily life. Therefore, we are still seeking treatment modalities with a better risk-benefit profile for patients with immune-mediated diseases.

It has been shown that healthy and pathogenic immune responses can be modulated by a variety of intrinsic or environmental regulators. For example, female predominance is found in many autoimmune diseases, and is likely to involve immunomodulation by sex hormones [1]. In patients with systemic lupus erythematosus (SLE), estrogen promotes development of the disease in genetically susceptible women by modulating key immune pathways, including type 1 interferon response. In contrast, progesterone suppresses pathogenic process of SLE by counteracting the effects of estrogen. This is evident by spontaneous improvement of the disease during pregnancy often seen in SLE patients. On the other hand, infection with helminths is shown to suppress autoimmune and inflammatory conditions in a setting of immune-mediated diseases, including inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis [2]. These immunomodulatory effects are mediated by a shift from T-helper 1 to 2 phenotype, promotion of regulatory T cell (Treg) induction, and a change from inflammatory cytokine to immunosuppressive cytokine profiles. Finally, it has been recognized that commensal bacteria are necessary for the development and maintenance of healthy immune system, and dysbiosis in the gut is actively involved in pathogenesis of many autoimmune and inflammatory diseases [3]. In this regard, recent reports have shown that Crohn's disease is successfully treated by transplantation of faces from healthy individuals [4]. These intrinsic or environmental regulators exert their immunomodulatory effects by intervening multiple checkpoints of the immune system, leading to correction of dysregulated immune responses without excessive immunosuppression. This review features potential immunomodulation strategies for immune thrombocytopenia (ITP), a typical organ-specific autoimmune disease.

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1. Pathogenic mechanisms of ITP and immunomodulation by intravenous immunoglobulin

Mechanisms for thrombocytopenia in ITP patients include increased platelet consumption and impaired platelet production, which are mediated through IgG anti-platelet autoantibodies reactive with platelet membrane glycoproteins, such as GPIIb/IIIa and GPIb/IX. Ongoing antiplatelet autoantibody response requires sustained activation of platelet glycoprotein-reactive $CD4^+$ T cells [5]. Based on the results from a series of in vitro assay for evaluating roles of GPIIb/IIIa-reactive $CD4^+$ T cells in antiplatelet autoantibody production, we have proposed a "pathogenic loop" model for the ongoing autoimmune response in ITP patients [6]. Namely, macrophages in the reticuloendothelial system, such as spleen, capture platelets opsonized by IgG antiplatelet antibodies via cell surface Fcγ receptors (FcγRs), and present antigenic platelet glycoprotein-derived peptides to T cells in the context of the major histocompatibility complex class II molecule. Autoreactive $CD4^+$ T cells to platelet glycoproteins are then activated by recognition of the antigenic peptides and exert helper activity to stimulate autoreactive B cells to produce IgG antiplatelet antibodies, which in turn bind to circulating platelets. The majority of current immunosuppressive regimens for ITP are aimed to interrupt this pathogenic loop, thereby suppressing production of IgG anti-platelet antibodies and increasing platelet counts. Specifically, corticosteroids suppress overall immune mechanisms, while splenectomy removes the major site for this pathogenic loop. Cytotoxic immunosuppressants, including cyclophosphamide and azathioprine, kill proliferating T and B cells upon activation, while cyclosporine selectively inhibits T-cell activation. Finally, rituximab depletes $CD20^+$ B cells that contain antiplatelet antibody-producing cells and antigen-presenting cells. These treatment modalities are often effective, but immunosuppressive effects are not specific to harmful autoimmune responses, leading to increased risk of severe infection.

Intravenous immunoglobulin (IVIG) is another treatment strategy effective for the majority of patients with ITP. The use of IVIG in treatment of ITP was first motivated by careful clinical observation by Imbach et al [7]. It has been shown that IVIG synergistically modulates disturbed immune responses through innate and adaptive immunity, involving macrophages, B cells, T cells, dendritic cells, and complements. These include blockade of activating FcγRs, activation of inhibitory FcγR, down-regulation of B cells by anti-idiotypic activity, suppression of T-cell activation through inhibitory cytokine release and increase in Tregs, and modulation of dendritic cell function, although the mechanisms of action are still incompletely understood [8]. Based on the synergistic mechanisms of action, efficacy of IVIG in immune-mediated disorders with similar pathogenesis as ITP has been studied extensively. As a result, IVIG is now used for treatment of many immune-mediated diseases, including those in neurology, dermatology, hematology, and rheumatology, and indications are still expanding. One of advantages of IVIG in clinical use is a good safety profile without excessive immunosuppression, which is likely to be explained by the complex mechanisms of immunomodulation involving multiple checkpoints. A practical example of IVIG with a wide range of indications strongly suggests that immunomodulation is a promising treatment strategy of many immune-mediated diseases.

2. Mechanisms of actions by *Helicobacter pylori* eradication

The increase in platelet counts in ITP patients after eradication of *Helicobacter pylori* was first reported by Gasbarrini and colleagues in 1988 [9]. After this discovery, many studies have been conducted worldwide to reproduce the efficacy of *H pylori* eradication in patients with ITP. Until now, meta-analyses have been independently conducted and revealed that *H pylori* eradication is closely related to platelet recovery in adult ITP patients [10–12]. Interestingly, the antiplatelet autoantibody response was suppressed and even disappeared after platelet recovery when *H pylori* had been successfully eradicated [13]. Recent long-term follow-up studies revealed that platelet increase in response to *H pylori* eradication lasted 8 or more years, with very few cases of relapse [14]. Thus, ITP appears to be clinically and immunologically cured by eradicating *H pylori* in a subset of ITP patients. Since *H pylori* eradication regimens are efficacious with good safety and economical profiles in adult patients with primary ITP, *H pylori* detection should be considered when diagnosis of primary ITP is made in adults, and the eradication therapy is recommended if *H pylori* infection is confirmed [15].

To elucidate mechanism by which *H pylori* eradication influences the ongoing pathogenic process of ITP, we have conducted a prospective study in which phenotype and function of circulating T cells, B cells, and monocytes are serially measured in *H pylori*–infected and –uninfected ITP patients treated with a standard eradication regimen [16]. At baseline, we found enhanced phagocytic capacity and low expression levels of inhibitory FcγRIIB in the circulating monocytes from *H pylori*–infected patients. This activated monocyte phenotype was suppressed after *H pylori* was successfully eradicated. Modulation of the FcγR balance toward an activating phenotype in macrophages has also been observed in *H pylori*–infected mice through a downregulation of inhibitory FcγRIIB. These findings indicate that the platelet recovery after *H pylori* eradication in ITP patients is mediated, in part, through a change in FcγR balance toward inhibitory FcγRIIB, which was also reported in the therapeutic action of IVIG for a mouse model of ITP [17]. In addition, several other mechanisms have been reported for promoting pathogenesis of ITP by *H pylori* infection. One intriguing theory is production of cross-reactive antibodies that react with both components of *H pylori* and platelet surface antigens through molecular mimicry [18]. In addition, chronic *H pylori* infection may act on the host's immune system to stimulate acquired immune responses, including activation of autoimmune-prone B-1 cells [19]. Moreover, some *H pylori* strains induce platelet aggregation that is dependent on the interaction of von Willebrand factor and IgG antibodies against *H pylori* with their corresponding receptors on platelets [20]. Changes of these immunologic responses after *H pylori* eradication together contribute to correction of the pathogenic loop of ITP, indicating that *H pylori* eradication is another immunomodulation for treating ITP.

3. Potential immunomodulatory effects by thrombopoietic agents

Thrombopoietin (TPO) regulates thrombopoiesis through the activation of megakaryocytes in the bone marrow, resulting in increased platelet production [21]. Recombinant TPO was first tried to use as a treatment for ITP patients, but clinical trials were halted because of its high immunogenicity [22]. Recently, a new class of thrombopietic agents, which are capable of binding to TPO receptor with high affinity, but do not have amino acid homologies to human TPO, have been developed and shown to be highly efficacious in patients with ITP [21]. These agents called TPO receptor agonists (TPO-RAs) include a peptibody romiplostim and a small molecule eltrombopag. It has been thought that TPO-RAs do not affect the autoimmune pathogenesis of ITP, since immunosuppressive or immunomodulatory roles of TPO had never been reported. Actually, in many ITP patients, platelet counts drop to the pretreatment levels immediately after treatment termination. However, we sometime experience ITP patients in whom platelet recovery was unexpectedly sustained even after