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Review

Small molecule phagocytosis inhibitors for immune cytopenias

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ABSTRACT

Immune cytopenias are conditions characterized by low blood cell counts, such as platelets in immune thrombocytopenia (ITP) and red blood cells in autoimmune hemolytic anemia (AIHA). Chronic ITP affects approximately 4 in 100,000 adults annually while AIHA is much less common. Extravascular phagocytosis and massive destruction of autoantibody-opsonized blood cells by macrophages in the spleen and liver are the hallmark of these conditions. Current treatment modalities for ITP and AIHA include the first-line use of corticosteroids; whereas, IVIg shows efficacy in ITP but not AIHA. One main mechanism of action by which IVIg treatment leads to the reduction in platelet destruction rates in ITP is thought to involve Fcγ receptor (FcγR) blockade, ultimately leading to the inhibition of extravascular platelet phagocytosis. IVIg, which is manufactured from the human plasma of thousands of donors, is a limited resource, and alternative treatments, particularly those based on bioavailable small molecules, are needed. In this review, we overview the pathophysiology of ITP, the role of Fcγ receptors, and the mechanisms of action of IVIg in treating ITP, and outline the efforts and progress towards developing novel, first-in-class inhibitors of phagocytosis as synthetic, small molecule substitutes for IVIg in ITP and other conditions where the pathobiology of the disease involves phagocytosis.

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Contents

1. Immune thrombocytopenia (ITP)

*I*mmune *t*hrombocyto*p*enia (ITP) is an autoimmune cytopenia characterized by a low platelet count in the absence of bone marrow-related or other abnormalities [1]. Patients suffering from ITP have an increased tendency to bleed, which can affect the skin and, in more severe cases,

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can result in bleeding from various mucous membranes. Internal bleeding complication can prove severe and sometimes fatal [2]. Acute ITP is common in pediatric populations but usually resolves spontaneously in less than a few months. Chronic ITP, which primarily affects adults, can last for 6 months or longer. Overall incidence of chronic ITP in the population is estimated at approximately 4 in 100,000 persons annually [3].

Generation of autoantibodies against various platelet antigens is a hallmark of ITP [4,5]. The mechanisms leading to the breakdown of tolerance in ITP are not entirely clear, but involve B cells, T cells and antigen-presenting cells [6]. Platelet opsonization by anti-platelet antibodies facilitates their extravascular destruction *via* antibody-mediated phagocytosis by the splenic macrophages in the spleen or by Kupffer macrophages in the liver [7,8]. Massive and ongoing loss of platelets underlies the resulting pathology. ITP autoantibodies against the collagen receptor (glycoproteins Ia/IIa or CD49b/CD29 or integrin $\alpha 2\beta 1$) [9], von Willebrand factor and thrombin receptor (glycoproteins Ib/IX or CD42a–d) [10], and fibrinogen receptor (glycoproteins IIb/IIIa or CD41/CD61) [11] have been documented. In the vast majority of cases, platelet autoantibodies bind either the CD41 or CD42 complexes [10,11].

2. Role of phagocytosis in ITP

Although some platelet destruction in ITP has been suggested to involve complement, the main mechanism of platelet destruction is phagocytosis that is mediated by mononuclear phagocytes. Fcγ receptors (FcγRs) can be both activating (FcγRI, FcγRIIA, FcγRIII) and inhibitory (FcγRIIB). Signaling by Fcγ receptors is mediated by immunoreceptor tyrosine-based activating (ITAM) or inhibitory (ITIM) motifs. Engagement of activating Fcγ receptors leads to receptor aggregation, phosphorylation of the ITAMs in the cytoplasmic tail of the receptor or in an associated adaptor protein by the Src-family tyrosine kinases, Fyn, c-Src and c-Yes, which then activate the spleen tyrosine kinase (Syk). This activation of intracellular signaling cascades in macrophages triggers phagocytic function [12–14]. The ITIM motif of the inhibitory FcγR, FcγRIIB, is associated with the tyrosine phosphatases, SHP-1 and SHIP-1, which downregulate the ITAM phosphorylation resulting in inhibition of the phagocytic signal [15].

A variety of the activating and inhibitory receptors expressed on phagocytes in the spleen (and liver) could be involved in the platelet destruction in ITP [16]. These FcγRs recognize autoantibodies, primarily IgG1 subclass [17], that are coating platelets in the affected individuals, which results in their phagocytosis and intracellular degradation in phagolysosomes. While increased platelet production can compensate for platelet destruction in ITP, the massive rate of platelet loss eventually overcomes compensatory megakaryopoiesis, which can also be affected in ITP [18], and results in the severely low platelet counts that are the hallmark of this disorder.

3. Intravenous immunoglobulin and other ITP treatment modalities

Treatment of ITP aims to promptly restore platelet counts in patients. Intravenous immunoglobulin (IVIg) and corticosteroids are standard first-line treatments for chronic ITP. IVIg is a purified immunoglobulin product, primarily consisting of IgG monomers, manufactured from pooled human plasma of thousands of donors [19]. IVIg was first used for the treatment of ITP in 1981 [20]. Clinic response rates to IVIg and corticosteroids are approximately 70% [21,22]. Thrombopoietin (TPO) mimetics and TPO receptor antagonists are used to maintain platelet levels in affected patients over the long term [23]. However, less than 15% of patients remain in remission. Laparascopic splenectomy can be used in these chronic ITP patients with curative outcomes, but a third of the patients still relapse [24]. Only some patients are able to discontinue TPO receptor antagonists and remain in remission [25].

A number of other treatment options are available for ITP, including general immunosuppression (cyclosporine), anti-Rh(D) antibodies, anti-CD40L, and FcγR-blocking monoclonal antibodies [26]. More treatments appear valuable but are still being evaluated, including rituximab (a B-cell-targeted anti-CD20 chimeric monoclonal antibody); however, despite good response rates, remission and infusion reactions associated with its use are still very common [27].

Despite new treatment modalities, the use of IVIg for ITP continues to be quite widespread. Based on one European retrospective analysis, IVIg is used in more than 50% of ITP cases, and in more than 12% first-line therapies [28]. Utilization of IVIg in ITP is projected to remain high and costs will remain significant. In Canada, the annual total cost of IVIg use per patient is estimated to exceed $100,000 [29], and the cost of IVIg use for ITP in the province of Ontario is projected at $5 million annually [30]. IVIg use in ITP in Canada only accounts for 8–17% of its use in all indications [30,31]. Finally, while IVIg use has a long clinical history and an excellent safety record, its use is not without side-effects, which could include, in mild cases, transient side-effects such as headache, nausea, fever, vomiting, cough, malaise, muscle, join and abdominal pain, flushing, urticarial lesions, and variations in heart rate and blood pressure, and in rare cases, leukopenia, neutropenia, and monocytopenia [32]. Severe side-effects following IVIg treatment are rare but have also been documented, and include aseptic meningitis, acute renal failure, stroke, exacerbation of pre-existing congestive heart failure, infections, life threatening hemolysis [33], deep venous thrombosis and pulmonary embolism [34], and anaphylactic shock [32]. The pursuit of alternatives to IVIg is thus of great interest. While a number of recombinant products are being evaluated as IVIg alternatives [35], the development of small molecule-based inhibitors stands to offer the greatest advantages with respect to both cost savings in manufacture and ease of administration.

4. Development of first-in-class small molecule inhibitors of phagocytosis for use in ITP

Because a number of mechanisms for IVIg activity have been suggested to play a role in the vast number of indications where it is utilized, developing a small-molecule alternative for IVIg is a disease-specific endeavor and necessitates the clear understanding of the IVIg mechanistic axis that is being tackled. Different mechanisms have been suggested to explain the efficacy of IVIg in ITP, but a dominant mechanism involves FcγR blockade [36,37]. Infused IVIg inhibits Fcγ receptors on mononuclear phagocytes, thereby interfering with their ability to phagocytose autoantibody-opsonized platelets. Even if the mechanism of IVIg in ITP is not FcγR blockade, the known pathophysiology of ITP (as for all immune cytopenias) involves phagocytosis as a major mechanism driving the destruction of platelets and provides strong rationale for the treatment of ITP *via* inhibition of phagocytosis. Thus, development of a small molecule inhibitor of phagocytosis is a viable strategy to replace or augment the use IVIg in ITP; and, could be applied for the treatment of other immune cytopenias.

While Fcγ receptors are promising targets in ITP, it is yet unclear which Fcγ receptor family should be optimally targeted to inhibit phagocytosis and treat human ITP. Some studies indicate that the shift in the balance of expression of various Fcγ receptors on patient monocytes towards inhibitory FcγR, as a result of treatment or infection, could have a significant effect on ITP outcomes [38,39]. Thus, both the inhibition of activating Fcγ receptors and activation of the inhibitory Fcγ receptors, or the underlying intracellular pathways, are attractive mechanistic targets. Fig. 1 outlines the potential modes of action of small molecule inhibitors of phagocytosis that could substitute for IVIg activity in ITP.

Early evidence that sulfhydryl and disulfide chemical groups were important for phagocytosis came from phagocytosis inhibition studies

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