Comment on Robak et al, page 3670

Are 25 antibodies better than 1?

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In this issue of Blood, Robak et al present data suggesting that rozrolimupab, a first-in-class mixture of 25 recombinant monoclonal IgG1 antibodies against RhD, has efficacy similar to plasma-derived anti-RhD in the treatment of immune thrombocytopenia.1

Plasma-derived anti-RhD, a hyper-immune preparation of IgG that targets the RhD antigen on erythrocytes, is a standard first-line therapy in nonsplenectomized RhD-positive individuals with immune thrombocytopenia (ITP), and is also used to prevent maternal RhD-sensitization and hemolytic disease of the newborn. The primary mechanism of action in ITP is thought to involve opsonization of endogenous RhD-positive red blood cells (RBCs), resulting in preferential clearance of antibody-coated RBCs by the reticuloendothelial system and sparing of antibody-coated platelets.2

In a phase 1/2 dose escalation study, rozrolimupab was administered as a single dose of 75 to 300 μg/kg to 61 nonsplenectomized, RhD-positive adults with primary ITP.1 Treatment was generally well tolerated. The most common adverse events, headache and infusion reactions, were predominantly mild and transient. As expected, most subjects experienced a fall in hemoglobin with a trend toward greater reductions with increasing dose. Across all dose cohorts, 21 patients (34%) achieved a platelet response (platelet count ≥ 30 × 10^9/L and increase from baseline of ≥ 20 × 10^9/L) at day 7. In general, response rates improved with increasing dose (see figure). In the 300 μg/kg cohort, 8 of 13 patients (62%) responded, a rate on par with the 60% to 72% response rate observed in clinical trials of plasma-derived anti-RhD.2

A recombinant replacement for plasma-derived anti-RhD offers several advantages. First, plasma-derived anti-RhD is produced by fractionation of IgG from pooled plasma of donors with high anti-RhD titers. Originally, most donors were RhD-negative RhD-positive women who had been immunized by pregnancy. Thanks to the widespread and effective use of anti-RhD prophylaxis, such women are now scarce and most donors today are RhD-negative hyperimmunized males. If this donor pool were to become compromised, availability of plasma-derived anti-RhD would be in jeopardy.3 Indeed, several countries including Australia and Poland have endured national shortages. A recombinant product would ensure a renewable source of anti-RhD. Second, although the risk of pathogen transmission with plasma-derived anti-RhD is very small, this risk would be all but eliminated with a recombinant product. Third, a recombinant preparation would eliminate rare adverse reactions due to impurities in plasma-derived anti-RhD such as transfusion-related acute lung injury or anaphylaxis in patients with IgA-deficiency.

The concept of monoclonal anti-RhD therapy for ITP is not new. Godeau et al treated 7 RhD-positive ITP patients with a single anti-RhD monoclonal antibody (MAB).4 Only 1 patient evinced a transient platelet response. Trials of RhD prophylaxis in RhD-negative subjects were similarly disappointing.1

Why would a mixture of 25 anti-RhD MABS, but not single MAB preparations, reproduce the effects of plasma-derived anti-RhD? The answer to this question is unknown, although several explanations are possible. An intuitive but probably incorrect
hypothesis is that a 25-MAB product is better equipped to target the antigenic diversity of RhD. Well over 100 mutations in RhD are known, many of which alter epitope topology. A mixture of MABs could be selected to target a number of these so-called “partial D” variants. However, the large majority of RhD-positive individuals (~98% of whites) are homozygous for wild-type 

RHD. The inclusion of MABs against rare partial D variants would therefore not be expected to dramatically affect response rates. Another hypothesis is that binding of antibody to multiple epitopes on RhD may enhance the immune response. Past studies suggest a synergistic effect on in vitro phagocytosis of opsonized platelets when anti-RhD MABs with different epitope specificity are combined. The mechanism by which this synergy may occur is uncertain, particularly given that RhD epitopes are small and overlapping and that antibody binding to a single epitope would be expected to block binding of antibody to other epitopes on the same RhD molecule. One wonders whether RBCs exposed to rozrolimupab have more bound anti-RhD than those exposed to a single MAB. A third hypothesis centers on epitope specificity. Previous work has shown epitope specificity to be a determinant of a given MAB’s ability to inhibit opsonized platelet phagocytosis in vitro. How epitope specificity affects this process is unknown, but could relate to the orientation of the MAB on the RBC surface and its interaction with Fc receptors. Perhaps the epitope specificity of 1 or more MABs in rozrolimupab, but not of the MAB tested by Godeau, engenders an inhibitory effect on platelet phagocytosis. To this end it would be of value to understand the individual effects on platelet phagocytosis of each of the component MABs in rozrolimupab. A fourth hypothesis holds that dosing of MAB in the Godeau study (47–95 μg/kg) may have been inadequate. Rozrolimupab showed a 5-fold lower potency than plasma-derived anti-RhD in vitro. A corresponding 4- to 6-fold higher dose (300 μg/kg) was required to achieve a similar clinical response to standard dose (50–75 μg/kg) plasma-derived anti-RhD. It may be that a single anti-RhD MAB with favorable epitope specificity at sufficient doses would yield a response similar to rozrolimupab.

Natural immune responses are polyclonal. It is thus tempting (but unproven) to surmise that a mixture of therapeutic MABs may be better than 1. If this assumption can be established and its mechanism elucidated, it could have far-reaching implications. Hyperimmune globulin preparations are used for passive immunization against a host of infectious diseases (eg, hepatitis B, cytomegalovirus, rabies). Mixtures of appropriately selected MABs against these organisms could replace plasma-derived therapy. The concept may also be applicable to cancer therapy. The epidermal growth factor receptor (EGFR) is dysregulated and is a validated therapeutic target in several malignancies. A mixture of 2 anti-EGFR MABs with different epitope specificities was recently shown to be superior to its component MABs alone in inhibiting cancer cell growth in vivo.

Rozrolimupab may someday offer a new therapeutic option for ITP. More importantly, it may represent a new paradigm for use of therapeutic antibodies, but we must first understand whether and why 25 are better than 1.

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REFERENCES


GENE THERAPY

Comment on Carbonaro et al, page 3677, and on Candotti et al, page 3635

Gene therapy for ADA-SCID: defining the factors for successful outcome

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In this issue of Blood, Carbonaro et al1 and Candotti et al2 demonstrate, in the clinical and nonclincial settings, the absolute need for cytoreductive conditioning in successful treatment of adenosine deaminase–deficient severe combined immune deficiency (ADA-SCID) by gene therapy. Intriguingly and in contrast to previously held paradigms, Carbonaro et al convincingly demonstrate that this disease can be corrected long term by gene therapy alone. Until now, the role of cytoreductive conditioning and the cessation of ERT, although thought empirically to be critical for successful gene therapy, have not been evaluated in a comparative manner.

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