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Is antibody therapy of tumor compromised by infusion-related reactions? A case for inhibiting the activity of cyclooxygenase-2

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Abstract

Evidence suggests that amelioration of childhood immune thrombocytopenic purpura and some other autoimmune states by intravenous normal IgG is due to the following chain of events: (1) cross-linking of Fcγ-receptors on blood effector cells; (2) release of mediators from these cells, often yielding an infusion-related reaction; (3) mediator-induced development of a cytokine field characterized by a mutually stabilizing Th2 polarization of CD4 T lymphocytes and alternative activation of macrophages; (4) selective quiescence of these macrophages towards targets coated with IgG autoantibody, due to increased expression of the macrophage Fcγ-receptor IIB. In this paper it is postulated that in the field of antibody therapy of tumor, an undesirable delayed or absent subsidence of antibody-coated tumor is due to immunomodulation of the same type as yields amelioration of autoimmunity, and arising from a similar chain of events. If the postulate is correct the chain could usefully be broken at the level of mediator action, possibly by blocking that increased synthesis of prostaglandin E_2 which is catalyzed by the enzyme cyclooxygenase-2.

Keywords: Immunomodulation; Antibody therapy; Tumor; Intravenous IgG; Prostaglandin; Fcγ-receptor; Cyclooxygenase-2; Macrophage alternative activation; Th2 polarization

1. Infusion-related reactions

Whenever an IgG antibody or a preparation of normal plasma IgG is given intravenously one must be prepared for an acute infusion-related reaction. Commonly this takes the form of rigors and fever during the infusion, sometimes accompanied by hypotension, bronchospasm, abdominal pain or other problems. In extreme cases the patient is at risk of multiple organ failure. But normally clinical experience indicates the degree of caution required for a particular reagent, and a slow infusion rate plus pre-infusion medication (often acetaminophen and an antihistamine) help keep reactions within tolerable limits. This article considers the mediators released during infusion-related reactions and how they may impede antibody therapy of tumor. Inferences are drawn from postulated analogous events occurring during the immunomodulation of autoimmune disease by large intravenous doses of normal human IgG (IVIG).

Preparations of IVIG, pooled from plasma of at least 1000 donors, are used in high dosage for two main purposes: to supply a wide range of anti-microbial antibodies to immunodeficient subjects and, of greater interest to us here, to inhibit by empirical means the tissue damage occurring in various autoimmune conditions. The preparations have been available since the early 1980s. To permit intravenous use the aggregated IgG, which was present in the old ethanol-precipitated intramuscular preparations, and capable of activating both complement and cells displaying Fcγ-receptors (FcγR), had to be largely removed. One criterion of effective removal was failure to activate complement in vitro [1]. However, IgG solutions satisfying this criterion can still contain small amounts of aggregate (Table 1). Due to its polyclonality IVIG is functionally complex [2]. Even after removal of obvious aggregates it is likely to contain alloreactive and idiotypically reactive antibodies, many probably cross-reactive in origin, which may induce a fluctuating content of small immune complexes in the preparation itself as well as inducing

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Table 1
WHO standards for intravenous IgG

≥90% Monomeric IgG
IgG subclass representation similar to that in normal serum
<5% Aggregates
<10% Split products
Free of pyrogens and vasoactive molecules
Minimal anti-complementary activity
No alloreactive red-cell agglutinins
Intact interactions with Fc-receptors and C1q
Biological $t_{1/2}$ >14 days

Adapted from [72].

formation of immune complexes after infusion. The reaction of certain rheumatoid factor antibodies with allotypic but not autologous epitopes on Fcγ is an example of what can happen here [3], with the infused IgG capable of acting as either antigen or antibody in the resulting complexes.

Doses of IVIG as high as 1 g/kg/day for 2 days are given in the treatment of childhood immune thrombocytopenic purpura (ITP). Although sometimes reported as well tolerated, several centres have described infusion-related reactions (headache sometimes accompanied by fever or vomiting, with occasional meningeal signs) in one-third or more of the patients [4–6].

Modern therapeutic antibodies for removing neoplastic cells, consisting commonly of monoclonal antibodies or derivatives thereof such as the chimeric antibody rituximab (anti-CD20), should be almost free of aggregates before infusion. Hence, the major source here of Fcγ-displaying aggregates leading to infusion-related reactions is likely to be post-infusion immune complexes containing the target antigen and the antibody. Anti-CD20 preparations given intravenously will encounter at least some normal B lymphocytes, so it is not surprising that a review of clinical trials of rituximab stated in 1999 that up to 94% of patients reported adverse reactions, although 90% of these were mild or moderate [7]. As would be expected severe reactions have occurred when the antibody's target cells, neoplastic B lymphocytes in the case of rituximab, are present in the blood in large numbers [8].

Whatever the source of Fcγ-displaying aggregates, both fluid-phase and cellular effectors are apt to be activated. The short-lived anaphylatoxin C5a is the principal inflammatory mediator released by activating complement [9], which may at least have a role in favoring activating rather than inhibitory FcγR on macrophages [10]. Apparently of more basic importance, as judged by experience with non-complement-activating bispecific antibodies whose effector arms target FcγR [11], is the cross-linking by Fcγ of these receptors on monocytes, granulocytes and NK cells in the blood. Thus activated the cells can produce a surge of potent, multifunctional, interacting mediators ([12–14] and Table 2). The phenomenon is often referred to as a "cytokine storm" although the more inclusive "mediator storm" would be better. Another possible source of mediators is the target cell itself. In this regard anti-CD3, often used to target T cells as part of an immunosuppressive cocktail in tissue transplantation, has posed a particular problem. Though less recognized for this property, B lymphocytes are also capable of responding to stimuli by releasing cytokines [15].

Table 2
Some inflammatory mediators secreted by activated granulocytes and macrophages

Class	Examples
Granule contents	Granzymes, histamine, TNF-α
Phospholipid derivatives	Platelet-activating factor Prostanoids: prostaglandins, prostacyclin, thromboxane Leukotrienes: B4, C4, D4, E4
Cytokines	IL-1, IL-6, IL-12, TNF-α CC and CXC chemokines
Reactive oxygen species	Superoxide, peroxide, hydroxyl
Reactive nitrogen species	Nitric oxide, nitrous anhydride

Whatever the type of antibody or IVIG evoking an infusion-related reaction, it commonly happens that the symptoms are worst for the first infusion of a series and lessen after that to disappear with repeated infusions (e.g. [16]). Sometimes an offending antigen in the blood will have been largely consumed by the initial infusions, but this explanation alone does not suffice and the 'first-pass' effect has not been fully explained. A significant contribution to it could arise from the infusion-related immunomodulation, which we proceed to discuss.

2. Infusion-related immunomodulation of autoimmune disease

After observing that the thrombocytopenia seen in two immunodeficient patients improved after giving IVIG to correct hypogammaglobulinemia, Imbach et al. [17] assessed the effect of this procedure in childhood ITP. They reported in 1981 [18] the remarkable finding that large amounts of IVIG, in this series 2 g/kg spread over 5 days (a total about twice the normal body content of IgG), can strikingly modulate the course of the disease. The platelet count rose sharply within 5 days, and in four of the six acute cases no further treatment was needed. Most of the cases of chronic or intermittent ITP needed repeated Ig infusions to maintain the platelet count, but sometimes these could be spaced weeks apart. So there is an impression that the underlying immunologic abnormality persists but that its manifestations are modulated. It appears also that this modulation is often prolonged sufficiently to cover the duration of the acute disease, the only ready alternative explanation being that a brief modulating process breaks a vicious cycle (such as antigen from damaged platelets stoking autoimmunization). Childhood ITP remains the most successful arena for high-dose IVIG but its use has been extended with some benefit to a number of other autoimmune and putative autoimmune conditions such as adult ITP, the Guillain–Barré syndrome, myasthenia gravis, dermatomyositis and Kawasaki's syndrome.