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Review

The implications of immunogenicity for protein-based multiple sclerosis therapies

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ABSTRACT

Administered proteins are inherently immunogenic, which may influence their efficacy or safety when used therapeutically. A review of the published literature was performed to compare and evaluate the development and consequences of antibodies against therapeutic protein agents for the treatment of multiple sclerosis (MS). Interferon beta (IFNβ), glatiramer acetate (GA), and natalizumab are all protein-based therapeutic agents approved to treat MS and are associated with the development of antibodies. Both binding antibodies and neutralizing antibodies (NAbs) develop to varying degrees in patients treated with any of the formulations of IFNβ. Comparison between studies is complicated by differences in methods, assays, criteria for determining NAb positivity, treatment duration, and fluctuation of NAb status. Despite these confounding factors, current data indicate that high-titer persistent NAbs may be relevant in terms of their effect on IFNβ bioavailability and bioefficacy. GA-reactive antibodies developed in a high proportion of GA-treated patients, but the clinical relevance of these antibodies remains to be established. Immunogenicity against natalizumab was associated with reduced efficacy and increased incidence of infusion reactions. Other emerging monoclonal antibody therapeutics have also been associated with the development of antibodies. Experience with generic biosimilars of other protein therapeutics suggests that the immunogenicity of generic biosimilar agents cannot be assumed and must be established for each formulation.

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1. Introduction

Endogenous proteins are protected from the host immune system by several mechanisms that result in self-tolerance (Fig. 1) [1]. Induction of immunologic tolerance to self-antigens can occur in primary lymphoid organs where lymphocytes are produced (ie, bone marrow and thymus) or in secondary lymphoid organs (ie, lymph nodes; spleen; and epithelium-based tissues in the gastrointestinal tract, skin, and respiratory system). Self-reactive lymphocytes are killed or inactivated because they do not normally receive costimulatory signals, which usually result from exposure to pathogens and are necessary for lymphocyte activation [1]. Receptor editing, which takes place in immature B-cells exposed to self-antigen in the bone marrow, is a mechanism whereby immature B-cells are stimulated to produce receptors that no longer recognize the self-antigen. Clonal deletion, or killing of self-reactive T-cells, can occur in both primary and secondary lymphoid organs. Inactivation of self-reactive lymphocytes, or clonal anergy, and suppression of the self-reactive T-cell by regulatory T-cells are other mechanisms of self-tolerance that occur when lymphocytes are exposed to self-antigen in secondary lymphoid organs [1].

When proteins are administered therapeutically, the human immune system may mount an immunologic response to the protein, such as has been observed with insulin, growth hormone, and factor VIII [2]. This immunologic response results from recognition of the protein as foreign and may break immune tolerance. Recombinant production of protein identical to the endogenous human amino acid sequence can reduce the risk of immunogenicity, but may not eliminate it because factors other than primary sequence contribute to immunologic potential [3]. Normally, antibody formation against endogenous human proteins is limited by the mechanisms involved in self-tolerance. Breaking of tolerance may result in development of antibodies against autoantigens or human proteins [4]. This immunologic response to protein-based therapies arises because the proteins are not exact replicas of the endogenous human protein. As a result, antibodies are formed that may or may not have an impact on a drug's therapeutic effect or cross-react with the action of the endogenous protein.

Several factors contribute to the immunogenicity of protein-based therapies (Fig. 2). Changes in the amino acid sequence, glycosylation, and tertiary structure of proteins with intrinsic immunomodulatory activity influence the immunogenicity of exogenously administered human proteins [5–7]. For heterogeneous or human chimeric proteins (eg, human-rodent chimeric antibodies), recognition of the protein as foreign is the primary basis for the antibody-mediated immunity [6,7]. Factors beyond the protein structure that contribute to immunogenicity include impurities arising from the production method; drug formulation; the route, dose, and frequency of administration; differences in major histocompatibility and human leukocyte antigen alleles among people; and the physiologic status of each person [6,7]. The rate of antibody formation is also influenced by the individual immune responsiveness. A study assessing the development of neutralizing antibodies (NAbs) in patients diagnosed with various diseases who were treated with interferon beta (IFNβ)-1b found that multiple sclerosis (MS) patients tended to have a higher incidence of IFNβ NAbs compared with cancer patients, suggesting that the immune response of MS patients may differ from patients with other disorders [8]. Detection of the immune response against a protein is also influenced by assay methods used to measure antibody levels, the antigen used in the assay, titers considered significant, and timing of testing in relation to dosing of the medication [5,6].

When discussing the immunogenic potential of a drug, certain terminology is used in the literature that should not be confused or used interchangeably with pharmacokinetic/pharmacodynamic language. *Antigenicity* is the property of a molecule to bind an antibody or T-cell receptor [9]. *Immunogenicity* generally refers to the property that endows a substance with the capacity to provoke an immune response or the degree to which a substance possesses this property [9]. *Bioavailability* is the degree to which a drug or other substance becomes available to the target tissue after administration [10]. *Bioequivalence* is the quality of having the same strength and similar bioavailability in the same dosage form as another specimen of a given drug substance [10]. *Bioefficacy* is the ability of a biologic to provide a desired therapeutic effect [10]. *Bioactivity* is the ability of a biologic to induce a biological response in vivo [10].

Whether antibodies against a therapeutic protein have clinically significant effects depends on the binding site of the antibody within the therapeutic protein [11], the affinity of the antibody for the therapeutic protein [12], and the titer of antibodies that develop [11]. For some protein-based therapies, the development of antibodies has no apparent clinical consequences, but for others, antibodies reduce therapeutic efficacy or are associated with therapy-related adverse events (eg, hypersensitivity, pure red-cell aplasia) [2,13]. The clinical significance of antibody development to protein-based therapies in the treatment of MS has been a topic of debate and concern. IFNβ revolutionized the treatment of MS by providing physicians with the first therapy shown to alter the disease course [14]. IFNβ reduces relapses and magnetic resonance imaging (MRI) activity in relapsing–remitting MS (RRMS), but it does not provide significant benefits in nonrelapsing secondary- or primary-progressive MS [14–16]. Three

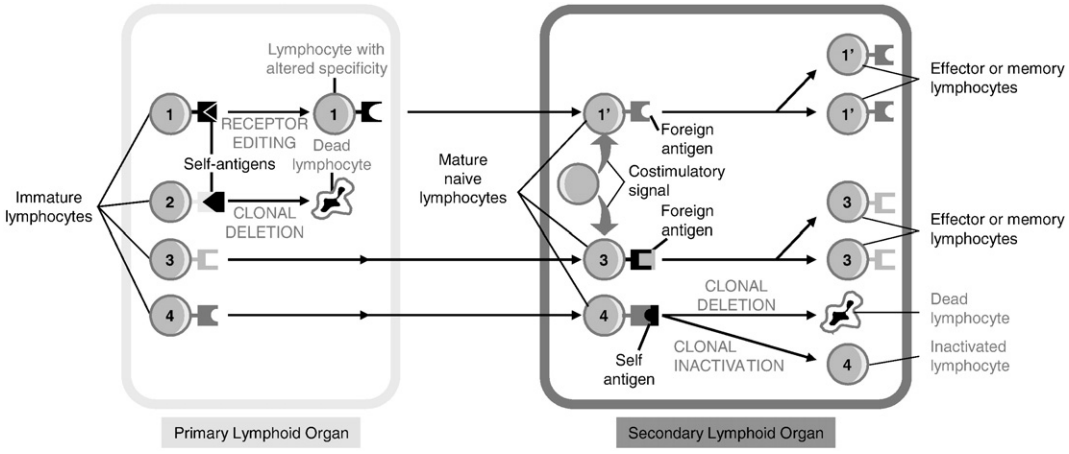

Fig. 1. Mechanisms of self-tolerance. Tolerance to self can be acquired as a result of several mechanisms, including inactivation of self-reactive lymphocytes (clonal inactivation or anergy), destruction of self-reactive lymphocytes (clonal deletion), or alteration of the receptors produced by the lymphocytes such that they no longer recognize self-antigens (receptor editing). (©2002 From Molecular Biology of the Cell, 5E by Alberts et al. Reproduced by permission of Garland Science/Taylor & Francis, LLC.).