Journal of Neuroimmunology 204 (2008) 1–12

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

B cell-targeted therapy with rituximab and autoimmune neuromuscular disorders

Joerg-Patrick Stübgen *

Department of Neurology and Neuroscience, Weill Medical College of Cornell University/New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065-4897, USA

ARTICLE INFO

Article history:
Received 13 May 2008
Received in revised form 22 July 2008
Accepted 25 July 2008

Keywords:
B cell depletion
Rituximab
Autoimmune polyneuropathy
Myasthenia gravis
Inflammatory myopathy

ABSTRACT

B lymphocytes play a central role in the pathogenesis of autoimmunity, so that B cell suppression is considered a potential treatment option for immune-mediated diseases. Rituximab, a chimeric anti-human CD20 antibody, is the only anti-B cell biological agent presently under study for the treatment of autoimmune neuromuscular diseases. Isolated case histories and series, pilot and retrospective studies report on the experimental administration of rituximab as treatment of a variety of immune-mediated neuropathy syndromes, treatment-refractory myasthenia gravis and inflammatory myopathies. Rituximab was used as monotherapy or in combination with other types of immunomodulation, and was well tolerated. The mechanism whereby B cell depletion shows benefit is uncertain and may vary depending on the inherent differences in the pathogenesis of various autoimmune neuromuscular disorders.

Contents

* Tel.: +1 212 746 2334; fax: +1 212 746 8742.
E-mail address: pstuebge@med.cornell.edu.

0165-5728/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneuroim.2008.07.019

1. B lymphocytes in autoimmunity

Improved understanding of the regulation of the immune system has elucidated a key role of B lymphocytes in the pathogenesis of many autoimmune diseases (Birnbaum et al., 2005; Dalakas, 2008). Based on the established immunobiological function of B cells in health, it is predicted that these cells support and perpetuate the autoimmune pathological process: (1) the presence of membrane-expressed immunoglobulin allows B cells to capture and concentrate proteins, including autoantigens, in an antigen-specific fashion; this enables B cells to function as highly efficient antigen-presenting cells, as they bind, internalize and process antigen, and re-express the processed peptides on their cell surfaces attached to major histocompatibility complex proteins; (2) B cells can produce cytokines (e.g., interleukin-4 and interleukin-10) and membrane-associated molecules that enlist and support activities of other mononuclear cells; (3) B cells may become involved in autoantigen-induced production of autoantibodies that are directly or indirectly (i.e., immune complex formation) destructive; (4) B cells may directly infiltrate endorgans (e.g., kidneys in lupus erythematosus and liver in mixed cryoglobulinemia); (5) B cells can evolve into autoreactive memory cells that remain relatively dormant for prolonged periods awaiting sequestered autoantigen re-exposure; (6) B cells may be triggered into disease-associated, uncontrolled clonal proliferation (or prolonged lifespan), and (7) B cells have the potential to differentiate into autoantibody-secreting plasma cells (Fig. 1).

In addition, autoantibodies contribute to autoimmunity by several mechanisms such as: (1) immune complex-mediated type III hypersensitivity reactions that depend on the interaction between antibodies and the complement system; (2) type II antibody-dependent cytotoxicity, and (3) instruction of innate immune cells to produce pathogenic cytokines such as interferon-α, tumor necrosis factor and interleukin-I (Chan et al., 1999; Cohen, 2005; Looney, 2006; Silverman and Weisman, 2003). The precise role of B cells and autoantibodies varies in different autoimmune diseases. The selective elimination of B cells became a feasible treatment option for various autoimmune conditions with the development of target-specific antibodies by hybridoma technology.

2. Antibody-based therapeutics

In 1975, Kohler and Milstein employed a method of somatic hybridization that generated “hybridoma” cell lines capable of producing monoclonal antibodies of defined specificities. Therapeutic monoclonal antibodies are currently approved for use in organ transplantation, percutaneous coronary intervention, chronic lymphocytic leukemia, acute myeloid leukemia, non-Hodgkin's lymphoma, breast cancer, colorectal cancer, rheumatoid arthritis, Crohn's disease, asthma, and prophylaxis of respiratory syncytial virus disease (Roskos et al., 2004). Molecular engineering technology has allowed the development of antibodies with a murine, chimeric human-murine, humanized, or fully human antigenic structure (Yan and Zhu, 2006). Antibodies act through multiple mechanisms that include: (1) modulating the function of key regulatory molecules and signaling pathways of tumor cells such as blocking growth factor/receptor interaction and/or down-regulating expression of oncogenic proteins; (2) recruiting effector mechanisms of the immune system such as antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity; (3) delivery of radionuclide or toxin payloads to target cells, (4) and other mechanisms such as anti-idiotype, catalytic antibodies, or antibodies that modulate a patient's immune response to tumors and autoantigens.

3. B cell-directed biological therapy

Effective targeting of B cells may be a beneficial therapeutic goal in various autoimmune diseases (Arkfeld, 2008; Edwards and Cambridge, 2006; Looney, 2005; Silverman and Weisman, 2003). Different biological approaches aimed at the B cell compartment are under investigation, such as antibodies directed against cell surface markers (CD20 and CD22) and a B lymphocyte stimulator (BLyS), and a fusion protein that neutralizes BLyS and a proliferation ligand (APRIL). B cell

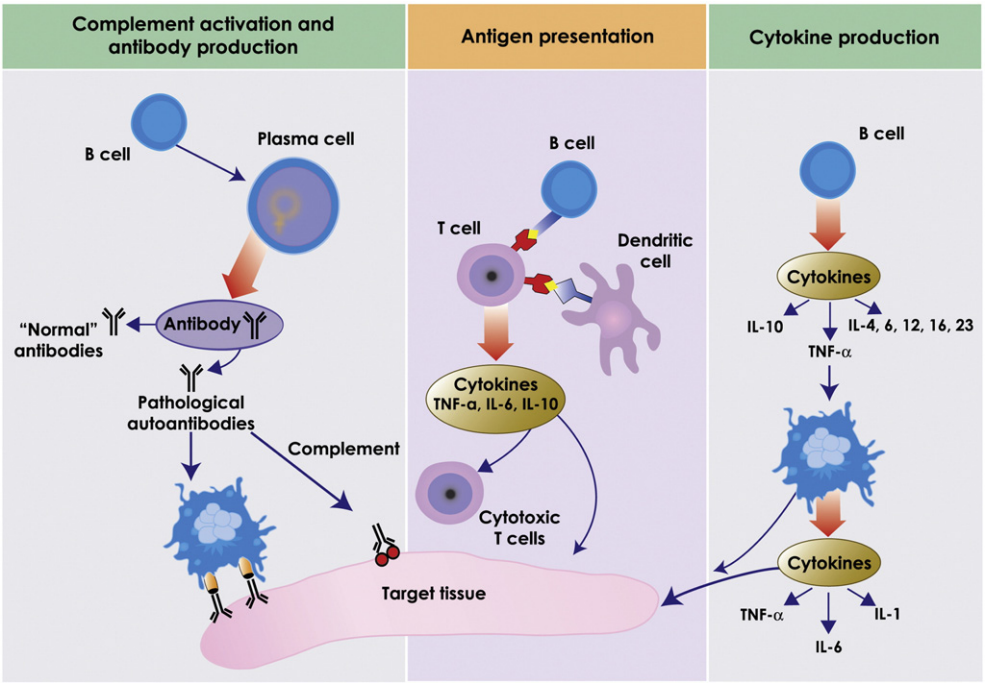

Fig. 1. B cells contribute to the pathology of immune-mediated conditions by antibody production, complement activation, or antibody binding to macrophages in an antibody-dependent-cell-mediated cytotoxicity (A); by acting as potent antigen-presenting cells resulting in clonal expansion of cytotoxic T cells (B); and by producing cytokines (interleukins, interferon-γ, and tumor necrosis factor-α), which affect activation of macrophages and various stages of immunoregulatory T cells (adapted from Dalakas, 2008).