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Review

Therapeutic strategies targeting B-cells in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) that traditionally has been considered to be mediated primarily by T-cells. Increasing evidence, however, suggests the fundamental role of B-cells in the pathogenesis of the disease. Recent strategies targeting B-cells in MS have demonstrated impressive and sometimes surprising results: B-cell depletion by monoclonal antibodies targeting the B-cell surface antigen CD20 (e.g. rituximab, ocrelizumab, ofatumumab) was shown to exert profound anti-inflammatory effect in MS with favorable risk–benefit ratio, with ocrelizumab demonstrating efficacy in both relapsing–remitting (RR) and primary-progressive (PP) MS in phase III clinical trials. Depletion of CD52 expressing T- and B-cells and monocytes by alemtuzumab resulted in impressive and durable suppression of disease activity in RRMS patients. On the other hand, strategies targeting B-cell cytokines such as atacicept resulted in increased disease activity. As our understanding of the biology of B-cells in MS is increasing, new compounds that target B-cells continue to be developed which promise to further expand the armamentarium of MS therapies and allow for more individualized therapy for patients with this complex disease.

Contents

1. Role of B-cells in multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that is characterized pathologically by inflammation, demyelination and axonal loss, and clinically by a variety of neurological signs and symptoms disseminated in time and space. MS has long been considered to be primarily a T-cell-mediated disease due to the observations of activated T lymphocytes in MS plaques, T-cell subset alterations in MS blood, and the fact that the animal model for MS, experimental autoimmune encephalomyelitis (EAE), can be passively transferred by myelin-reactive T cells. Although the intrathecal synthesis of oligoclonal immunoglobulins has been recognized for decades, B-cells and antibodies (Ab's) have been neglected in MS research due to their indispensible role in EAE and the lack of suitable technology to investigate them. Recent advances in flow cytometry and DNA sequencing methods unveiled the fundamental contribution of B-cells, plasma cells and their products in immune responses and their central role in the pathogenesis of MS as well as other immune-mediated disorders: plasmablasts and plasma cells can produce autoantibodies recognizing surface myelin antigens, which can be pathogenic and initiate an

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acute inflammatory cascade by complement activation. Antibodies can also induce tissue injury by binding to Fc receptors on macrophages, neutrophils and NK cells, and attack their targets via an antibody-dependent cell-mediated cytotoxic process. Autoreactive B-cells can function as effective and specific antigen-presenting cells (APC) and activate their cognate autoreactive T-cells through the trimolecular complex and costimulatory molecules. Such B-cell–T-cell interactions result in simultaneous expansion of antigen-specific B- and T-cells that enhance the immune response and promote disease. B-cells from MS patients show exaggerated pro-inflammatory response to activating stimuli and may contribute to abberant T-cell activation and autoimmunity through "bystander activation" by secreting pro-inflammatory cytokines. Regulatory B-cells (Bregs) secreting interleukin (IL)-10, which normally maintain homeostasis and protect from autoimmunity, are deficient in MS, and thus contribute to unchecked autoimmunity. Finally, lymphogenesis supported by B-cell cytokines and chemokines in the brain may promote ongoing local immune injury [1–4]. The possible contribution of B-cells to MS pathogenesis is supported by observations of (I) pathologic heterogeneity of MS lesions (with pattern-II, antibody-mediated demyelination, being the most common one) [5]; (II) the formation of meningeal B-cell follicles in secondary-progressive MS [6], which is associated with early disease onset and severe cortical pathology [7]; (III) the presence of dominant B-cell clonotypes, compatible with an antigen-selection process as well as antibody-secreting plasmablasts and plasma cells in the CSF and lesions of MS patients (the numbers of which correlate with local IgG synthesis and the extent of CNS inflammation), along with immunoglobulins (predominantly IgG1) and B-cell cytokines [8]; and (IV) the beneficial effect of B-cell targeted therapies in MS.

2. Therapies targeting CD20

The CD20 molecule is expressed on most cells of the human B cell lineage, from pre-B and immature B cells through naïve and memory B cells, but not on stem cells, pro-B cells, or differentiated plasma cells [9]. Several monoclonal antibodies (mAbs) targeting CD20 can deplete B-cells by mechanisms of complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and induction of B-cell apoptosis. Three such mAbs have been tested in MS: (I) rituximab (Rituxan, Genentech and BiogenIdec, RTX), a chimeric mAb approved for the treatment of B-cell lymphoma and rheumatoid arthritis (RA); (II) ocrelizumab (Roche/Genentech), a humanized mAb that binds to a different but overlapping epitope compared with rituximab and depletes B cells primarily through ADCC, rather than by a CDC mechanism, possibly with greater efficacy than rituximab; and (III) ofatumumab (Arzerra, Novartis Oncology), a fully human mAb with a very low immunogenic risk profile that binds to a completely distinct epitope, dissociates more slowly from the CD20 antigen, and exhibits pronounced CDC activity and relatively decreased ADCC. Ofatumumab is approved for the treatment of chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab.

2.1. Rituximab

Rituximab was evaluated in a 48-week double-blind placebo-controlled phase II clinical trial in 106 patients with relapsing–remitting (RR) MS (Table 1) [10]. Patients received a single course of 1000 mg rituximab or placebo administered intravenously on days 1 and 15. The mean number of T1 gadolinium-enhancing (Gd+) lesions on MRI scans (the study's primary endpoint) was reduced at 24 weeks by 91% compared to placebo ($p < 0.001$). The mean number of new Gd+ lesions was reduced by 95% ($p < 0.001$). These results were sustained for 48 weeks ($p < 0.001$). There was a significant reduction in the proportion of patients with relapse at week 24 (14.5% vs. 34.3%, $p = 0.02$) and 48 (20.3% vs. 40.0%, $p = 0.04$). Infusion-associated adverse events, mostly mild to moderate in severity, were more frequent in the rituximab group and decreased in frequency and intensity from the first to the second infusion. No differences were observed in the incidence of serious adverse events or infections between rituximab- and placebo-treated groups, and no clinically significant opportunistic infections were reported. Human anti-chimeric antibodies (HACA) against rituximab found in 24.1% of the treated patients at week 48 were not associated with the type or severity of adverse events, or the efficacy measures throughout the study.

In another phase II/III clinical trial, 439 primary-progressive (PP) MS patients were randomized at a 2:1 ratio to receive 4 courses of two 1000-mg intravenous rituximab or placebo infusions every 24 weeks, through 96 weeks (Table 1) [11]. Although the time to confirmed disability progression (CDP) sustained for 12 weeks (the primary endpoint) did not reach statistical difference, rituximab patients had less increase in T2 volume load on MRI ($p < 0.001$). Subgroup analysis showed that time to CDP was delayed in patients aged <51 and those with Gd+ lesions in the rituximab group compared with placebo, suggesting a beneficial effect of B-cell depletion in younger PPMS patients with inflammatory activity. Infusion-related events, predominantly mild to moderate, were more common with rituximab during the first course, and decreased to rates comparable to placebo on successive courses. Serious infections occurred in 4.5% of rituximab and 1.0% of placebo patients. Experience with rituximab in other autoimmune diseases and malignancies raised concerns about serious bacterial, fungal or viral infections, including progressive multifocal leukoencephalopathy (PML) and the reactivation of hepatitis-B virus, as well as serious mucocutaneous reactions [4].

Despite these results, Roche and Genentech decided not to advance trials of rituximab in MS and opted instead to focus on ocrelizumab, a humanized anti-CD20 mAb with better biological properties and reduced immunogenicity.

2.2. Ocrelizumab

Three phase III clinical trials with ocrelizumab in MS have been presented at the recent European Committee on Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress in Barcelona:

OPERA I and II were two identical phase III, multicenter, randomized, double-blind, double-dummy, parallel-group trials that randomized (1:1) a total of 1656 relapsing patients to receive ocrelizumab 600 mg via intravenous infusion every 24 weeks or interferon (IFN)-β-1a 44 μg subcutaneously three times per week throughout a 96-week treatment period (Table 1) [12]. The primary endpoint—annualized relapse rate at 96 weeks—showed a 46% to 47% reduction with ocrelizumab compared with IFN-β-1a ($p < 0.0001$). Both studies also showed a 40% reduction in 12- and 24-weeks confirmed disability progression, a 94% to 95% reduction in the number of Gd+ lesions and a 77% to 83% reduction in the number of new/enlarging T2 hyperintense lesions on MRI. Brain volume loss was reduced by 23.8% with ocrelizumab vs. IFN-β-1a, and the number of patients with "no evidence of disease activity" (NEDA) increased from 25% with IFN-β-1a to 48% with ocrelizumab.

The ORATORIO trial randomized (2:1) 732 patients with PPMS who had an elevated cerebrospinal fluid IgG index or one or more oligoclonal bands to ocrelizumab (two infusions of 300 mg separated by 14 days every 24 weeks) or placebo for 120 weeks (Table 1) [13]. Ocrelizumab significantly reduced CDP sustained for at least 12 weeks (primary endpoint) by 24% ($p = 0.0321$) and CDP sustained for at least 24 weeks (secondary endpoint) by 25% ($p = 0.0365$). Additional secondary endpoints were also reached, including change in time to walk 25 ft from baseline ($p = 0.04$), change in T2 lesion volume from baseline ($p < 0.0001$) and rate of brain volume loss ($p = 0.02$).

The most common adverse event in all 3 studies was infusion-related reactions. Serious adverse events did not differ between groups, and there were no opportunistic infections or cases of PML. Six malignancies were reported in the OPERA trials (2 in IFN-β-1a arm and 4 in ocrelizumab arm), and 13 malignancies occurred in the ORATORIO