Review

B cell targeted therapy in autoimmunity

Miri Blank, Yehuda Shoenfeld

Abstract

Autoimmunity results from a break in self-tolerance involving humoral and/or cell-mediated immune mechanisms. Part of the pathological consequence of a failure in central and/or peripheral tolerance, results from survival and activation of self-reactive B cells. Such B cells produce tissue-damaging pathogenic autoantibodies, and subsequent formation of complement-fixing immune complexes that contribute to tissue damage.

Current pharmacological strategies for treating autoimmune diseases involve global use of broad-acting immunosuppressants that with long term use have associated toxicities. The present drive in drug development is towards therapies that target a specific biological pathway or pathogenic cell population. This review focuses on some of the emerging therapies based on co-stimulation blockers, and compounds which contribute to a specific B cells depletion, based on studies in animal models and human clinical studies.

1. Introduction

In recent years, data have emerged suggesting that B lymphocytes play a broader role in immune responses and are not merely the passive recipients of signals that result in differentiation of antibody-producing plasma cells. Along with their traditional roles as antigen presenting cells and precursors of antibody-producing plasma cells, B cells have also been found to regulate antigen presenting cells (APCs) and T cell functions, produce cytokines, and express receptor/ligand pairs that previously had been thought to be restricted to other cell types [1]. Autoimmunity results from a breakdown of self-tolerance involving humoral and/or cell-mediated immune mechanisms in. Among of the consequences of failure in central and/or peripheral tolerance, are survival and activation of self-reactive B cells. Such B cells produce pathogenic autoantibodies, which can form complement-fixing immune complexes that contribute to tissue damage.

Several humoral autoimmune diseases, are defined by excessive activation of both B and T lymphocytes. Activation of these cells requires in cooperation, antigen engagement and co-stimulatory signals from interacting lymphocytes [2]. Thus, blockade of co-stimulatory signals offers therapeutic approach in some autoimmune conditions. Other therapeutic approaches are based on the fact that signals from the B cell receptors help determine the B-cell fate, leading to proliferation, differentiation, growth arrest or apoptosis [3–6].

2. Blockade of co-stimulatory signals

Some of the most biologically important signals that B cells receive from activated cognate T cells are delivered through membrane-bound tumor necrosis factor (TNF) and TNF receptor families of proteins. Currently, considerable interest is

* Corresponding author. Department of Medicine B, Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel.: +972 3 530 2652; fax: +972 3 53 528. E-mail address: shoenfel@post.tau.ac.il (Y. Shoenfeld).
focused on the development of modulators of B cell activation through these surface receptors. Several novel therapeutic agents that interfere in the co-stimulatory signals were introduced and found to delete autoreactive lymphocytes and block autoimmune disease progression. These developed co-stimulation blocker include: monoclonal antibodies (mAbs) directed to the receptor or to the receptor ligand, fusion proteins or DNA vaccination summarized in Table 1.

Lymphocyte activation requires costimulatory signals such as those provided by the CD28/B7 and CD40/CD40L.

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Table 1
B cell targeting in autoimmune diseases

receptor-ligand pairs [7,8], B7/CD28 co-stimulatory pathway is one of the major regulatory pathway for the control of immune responses. B7-1 and B7-2 are the main ligands for CD28 (a positive regulator of T cell activity). The cytotoxic T-lymphocyte antigen-4 (CTLA4)(CD152), expressed on activated T cells, a strong negative regulator of T cell activity, is an additional ligand for B7. The following compounds were developed addressing these molecules.

2.1. CTLA4Ig fusion protein

CTLA4Ig is a soluble molecule composed of the extracellular domain of the CTLA4 (CD152) fused to an immunoglobulin IgGFc domain. It binds B7 ligands on B cells with 20-fold greater affinity than CD28, thereby blocking the binding of CD28 to B7-1 (CD80) or B7-2 (CD86) and inhibiting T cell priming. Long-term administration of CTLA4Ig as a fusion protein or expressed in adenovirus, to NZB/NZW F1 mice, prevented the onset of lupus-prone NZB (SNF1), lupus-prone NZW F1 mice [14,15], in collagen-induced arthritis [16], experimental allergic encephalomyelitis [17], and chronic graft-vs-host disease [18]. Clinical studies with CTLA4Ig fusion protein showed improvement in rheumatoid arthritis activity when added to methotrexate therapy [12].

2.2. DNA co-vaccination with B7-1wa

A single substitution in amino acid in B7-1 (B7-1wa), abrogate the binding of B7-1 to CD28 but not to CTLA4. Thus, B7-1Ig was inhibitory for CTLA-4L [12]. In-vivo, gene transfer of co-injection of a B7-1wa (membrane-bound form) plasmid blocked induction of anti-CEA immunity. DNA covaccination by co-injection of a B7-1wa (membrane-bound form) plasmid into non-obese diabetic (NOD) mice with autoimmune diabetes abrogated reactivity to insulin and ameliorated the disease through cDNA encoding selective CTLA-4L (the B7-1wa) [12].

2.3. Anti-CD40L mAb

CD40 and its ligand CD40L (CD154) [13]. The interaction of CD40L on activated T cells with CD40 on B cells induces B cell proliferation, differentiation, APC activation, cytokine secretion and formation of germinal center and IgG switching [13]. Studies in murine models using anti-CD40L mAbs as a costimulatory blockade, showed effective delay in disease onset in lupus mouse models such as SWR × NZB (SNF1), NZB × NZW F1 and MRL lpr/lpr mice [14,15], in collagen-induced arthritis [16], experimental allergic encephalomyelitis (EAE) [17], and chronic graft-vs-host disease [18]. Clinical studies using humanized anti-CD40L in lupus patients markedly reduced the frequency of IgG anti-DNA antibody-producing B cells, which persisted for several months after cessation of treatment [19]. Recent data from an open-label study of a humanized anti-CD40L mAb in the treatment of patients with active SLE nephritis have shown decreases in serum titer of anti-dsDNA antibody levels, proteinuria, and SLE Disease Activity Index (SLEDAI) scores [20]. Anti-CD40L mAb (IDEC-131) was tested also in other autoimmune conditions such as SLE, idiopathic thrombocytopenic purpura (ITP), in Crohn’s disease [21]. Phase II clinical studies were conducted and no further development has been reported.

2.4. Anti-CD40 mAb (5D12)

A chimeric immunoglobulin containing the variable domains of the heavy and light chains of the murine version of 5D12, antagonist of the CD40-CD40L pathway [22]. This new chimeric mAb was tested successfully in an experimental autoimmune encephalomyelitis model in cynomolgus monkeys [23].

2.5. Soluble CD40L

Many cell-membrane proteins are subjected to limited proteolysis (called shedding) that gives rise to soluble forms consisting of extracellular domain of the protein [24]. Elevated levels and functional capacity of soluble CD40L was detected in SLE sera and rheumatoid arthritis (RA) plasma [25,26]. A recombinant human soluble CD40Ligand was developed for targeting the CD40L.

2.6. Anti-4-1BB (CD137) mAb

4-1BB (CD137), a member of the tumor necrosis factor (TNF) receptor superfamily, is a costimulatory molecule [27] primarily expressed on activated T cells and natural killer (NK) cells. Its natural ligand, 4-1BBL (CD137L), has been detected on macrophages, dendritic cells and resting B cells. 4-1BB ligand can costimulate human CD28- T cells, resulting in cell division, inflammatory cytokine production, increased perforin levels, enhancement of cytolytic effector function, as well as the up-regulation of the anti-apoptotic protein Bcl-X(L) [28]. Promising treatments with anti-4-1BB were tested in autoimmune animal models (Table 1). Fas deficient MRL/lpr mice treated with an agonistic anti-4-1BB mAb, specific for costimulatory molecules, blocked lymphadenopathy, skin lesions, reduced anti-DNA Ab production, attenuated nephropathy leading to prolonged survival and blocked the progression of the spontaneously developed autoimmune state [29]. Anti-4-1BB mAbs treatment reversed acute disease lupus-prone NZB × NZW F1 mice, and extended the mice lifespan from 10 months to more than 2 years [30]. Furthermore, injection of humanized anti-4-1BB mAbs into non-human primates suppressed the development of T-dependent humoral immunity [31].

2.7. Anti-BLyS mAb

BLyS (B lymphocyte stimulator) is a B cells targeting the peripheral B cell survival factor that belong to the TNF family, also known as BAFF (B cell activating factor), or TALL-1 (TNF and apoptosis ligand-related leukocyte-expressed ligand 1) to THANK (TNF homologue that activate apoptosis, NFkB and Jun NH2-terminal kinase) and zTNF4, plays a crucial role
of BLyS [44]. LymphoStat-B was developed as a potential that specifically recognizes and inhibits the biological activity of BLyS for the treatment of systemic lupus erythematosus, rheumatoid arthritis, and autoimmune diseases [45,46]. The receptors for BLyS are: two orphan receptors that belong to the TNF receptor family, transmembrane activator and calcium-modulating and cyclophilin ligand (CAML) interactor (TACI) and B cell maturation protein (BCMA) [37]. BCMA is B cell specific, whereas TACI is expressed on activated T and B cells, and bind the proliferation-inducing ligand (APRIL). However, preferred binding was observed with TACI- BLyS and BCMA-APRIL pairs [32,33]. Considerable body of evidence implicating BLyS in the induction of B cell autoimmunity paved the way for developing therapeutic strategies in several animal models of autoimmune diseases and proved to be effective [42,43].

LymphoStat-B (tm) is a human monoclonal antibody (scFv), that specifically recognizes and inhibits the biological activity of BLyS [44]. LymphoStat-B was developed as a potential treatment for systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases [45,46]. LymphoStat-B inhibits the binding of BLyS to its 3 receptors, TACI, BCMA and BR3. It significantly reduces the levels of circulating B (CD20) cells in mice and cynomolgus monkeys. BLyS antagonist TACI-Fc and BR3-Fc (BAFFR-Fc), BCMA-Fc were generated using a decoy receptor-Fc fusion protein. TACI-Fc and BR3-Fc were found to delay the onset of autoimmunity in at least one mouse model of lupus in NZB × W F1 and MRL-lpr/lpr mice [37,43]. BCMA-Fc ameliorated experimental lupus models and experimental autoimmune encephalomyelitis [32,33], Table 1. Treatment of B6-lpr/lpr mice with adenovirus-encoded soluble TACI, Ad/TACI-Fc, resulted in elevated serum levels of TACI-Fc protein and inhibition of ongoing autoimmunity [32,33]. Promising results were obtained in additional autoimmune animal model of collagen II -induced arthritis in DBA/1j mice [45].

3. Selective B cell depletion

3.1. Anti-CD20 mAbs Rituximab

Selective B lymphocyte depletion has been made possible by the availability of the chimeric anti-CD20 mAb Rituximab [46–48]. CD20 is a B lymphocyte-restricted antigen that is expressed on B lymphocyte precursors and mature B lymphocytes. It is lost during differentiation into plasma cells. In autoimmune diseases, Rituximab has been used in many cases as monotherapy [49–52], or as combined therapy with other drugs such as cyclophosphamide, corticosteroid, intravenous immunoglobulin (IVIG), plasmapheresis and other immunosuppressive agents [53–59] (Table 1).

3.2. Anti-CD22 mAbs Epratuzumab

CD22 is first expressed in the cytoplasm of pro-B and pre-B cells, and on the surface of B cells mature to become IgD+. It has a role in intercellular interactions, activate B cells and modulate antigen receptor signaling in vitro [60]. Humanized anti-CD22 mAbs block CD22 adhesive function, particularly in diverse autoimmune disease (Table 1) [48,60,61].

4. Specific molecular targeting of B cell antigen receptor — BCR

Signals generated through the B cell antigen receptor (BCR) are critical to development and B cell responses to antigen. Defective BCR signaling can result in immunodeficiency as well as a predisposition to autoimmunity. The BCR is a multiprotein complex containing an antigen-binding membrane immunoglobulin (Ig) generated via rearrangement and assembly of heavy and light chains. The generation and maintenance of self-reactive B cells is regulated by autoantigen signaling through the BCR complex. Engagement of the BCR initiates a cascade of signaling events resulting in the induction of cell proliferation, differentiation, anergy or apoptosis. Autoimmune state can be modulated through BCR targeting. The classical molecules controlling the BCR expression are the anti-idiotypic mAbs leading to specific apoptosis by anti-dsDNA anti-idiotypic mAbs [61,62].

4.1. Intravenous immunoglobulin — IVIG

IVIG is a pooled normal polyclonal IgG obtained from plasma of several thousand healthy donors increasingly being used as an immunomodulatory therapy for patients with autoimmune diseases [63–68] (Table 1). Although the precise mechanism of action of IVIG in autoimmunity is unknown, one of the dominant hypothesis is that it involves manipulation of the idiotypic network by neutralization of pathogenic autoantibodies via blocking the idiotypes (e.g. IVIG composed of a cohort of anti-idiotypic Abs characterizing a panel of autoimmune diseases). This hypothesis is supported by studies in murine experimental models (Table 1). Administration of IVIG to these autoimmune mice resulted in abrogation of the clinical manifestations of SLE and prevented fetal loss in APS via immunoregulation of the idiotypic network [69–71].

Recently, we have generated affinity purified lupus specific enriched fraction of anti-idiotypic polyclonal Abs from IVIG preparation, using a column constructed from affinity purified anti-dsDNA from 55 patients with SLE designated superIVIG (sIVIG). Administering this sIVIG to lupus mice, NZB × NZW F1, resulted in an amelioration of the diverse lupus manifestations (e.g. decrease in the titers of anti-dsDNA, proteinuria, and glomerulonephritis), 200 times more effective than IVIG [72]. sIVIG specific to another autoimmune disease, APS, was recently produced by us by passing IVIG on
a column composed of anti-beta 2-glycoprotein-I (β2GPI) Abs derived from 15 patients [73]. These results open a new path for developing IVIG specific to different autoimmune diseases, targeting the BCR.

4.2. BCR specific synthetic peptides

By employing hexapeptide phage display library and anti-β2GPI mAbs, we were able to identify peptides which are mimetics of anti-β2GPI target epitopes in APS [78]. These peptides on a poly-L-Lysine backbone were able to cause a specific CD19 B cell apoptosis via BCR targeting [75]. LJP 394 also called Abetimus or Riquent, is a synthetic toleragen molecule consisting of four double-stranded oligodeoxyribonucleotides attached to non-immunogenic polyethylene glycol, a proprietary carrier platform. In patients with high-affinity Abs to its DNA epitope it prolonged the time to renal flare, decreased the number of renal flares, and required fewer HDCC treatments compared with placebo [79]. Branched peptides composed of beta-2-glycoprotein-I derived peptides, were found to be effective in specific B cell depletion also in antiphospholipid syndrome [77,80].

4.3. Enhancement of inhibitory Fc receptor (FcγRIIB) expression on B cells

The ability of FcγRIIB to couple the BCR and promote the B cell to an inhibitory pathway, can potentially determine the fate of B cells upon IgG immune complex engagement. Deficiency of RIIB on B cells leads to autoimmune disease in specific genetic backgrounds [81–84]. Lupus, a multigenic autoimmune condition in which a breakdown of tolerance results in the development of autoantibodies, leads to a variety of pathologic outcomes. FcγRIIB regulates a common B cell checkpoint in genetically diverse lupus-prone mouse strains, and modest changes in its expression can result in either tolerance or autoimmunity [81–84]. Therefore, increasing FcγRIIB expression on B cells may be an effective way to treat humoral mediated autoimmune diseases. Recently, the group of Ravetch V [82] demonstrated that mice that received FcγRIIB retroviral-transduced bone marrow cells, exhibit reduced levels of serum antinuclear antibodies (ANAs), antibodies to DNA, or antibodies to chromatin, when compared with mice that received autologous bone marrow transduced with the parent retrovirus. Renal function in NZM or BXSB mice whose marrow was reconstituted with marrow that was transduced with the FcγRIIB retroviral constructs, was comparable to that of wild-type mice, with the majority showing little to no proteinuria. In contrast, the majority of control exhibited a marked reduction in their kidney function associated with severe proteinuria. Histological examination showed that the kidneys of FcγRIIB retroviral-transduced mice resembled those of healthy mice, and untreated or mock-transduced NZM2410 and BXSB mice exhibited substantial renal pathology with proliferative glomerulonephritis, tubulo-interstitial inflammation, and pronounced glomerular sclerosis. Similarly, FcγRIIB retroviral transduction significantly reduced vasculitis and lung inflammation in NZM 2410 mice as compared with the control groups [83,84]. This proposed concept of elevation of the B cell expression of the inhibitory FcγRIIB receptor theoretically can be adapted to other autoimmune conditions with decreased expression of FcγRIIB.

5. In conclusion

B cell targeting therapy seems a potential specific approach for various autoimmune conditions apparently associated with very low side effects.

References


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