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Novel therapeutic approaches in systemic lupus erythematosus

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1. ABSTRACT

Systemic lupus erythematosus is a prototypical systemic autoimmune disease, affecting multiple organs and organ-systems, leading to a wide variety of symptoms, serological and clinical features. The pathogenesis of the disease encompasses a complex interplay among various immune-competent cells and inflammatory mediators, which gives ground to target numerous potentially harmful players in this system. The aim of the present review was to depict certain aspects on the pathogenesis of SLE and to highlight pathways that can be promising targets of novel therapeutic approaches. T-cell, B-cell targeting, modification of co-stimulatory pathways, anti-cytokine therapy, soluble mediators, as well as autologous stem cell transplantation have been addressed. Finally, we described potential side effects of these biologics.

2. INTRODUCTION

The clinical entity, systemic lupus erythematosus (SLE) encompasses a group of heterogeneous, systemic autoimmune diseases, including mild-to moderate forms and severe, progressive variants as well (1). Accordingly, the management of lupus is still remaining challenging. Although survival of lupus patients has increased in the past decades, there are patients, who do not respond to traditional immune suppressive therapies. Furthermore, conventional therapies, including corticosteroids and cyclophosphamide, can be effective but at an unacceptable cost and adverse effects (2). In the last few years, novel immune suppressive therapies in lupus have been launched with more selective immune modulating effects and safer toxicity profiles.

The aim of the present review was to depict certain aspects on the pathogenesis of SLE and to highlight pathways that can be targets of novel therapeutic approaches.

Recent advances in our understanding of lupus pathogenesis have suggested new, targeted therapies. Due to genetic and environmental influences, a complex dysregulation of the immune system develops, leading to the loss of self-tolerance. These processes are driven by the intricate interplay among antigen-presenting cells (APCs), members of the native and adaptive immune system, conducted by a disproportional, pro-inflammatory cytokine/chemokine milieu (3). It has become clear that B lymphocytes play a key role in disease development by pathogenic autoantibody production and also by antibody-independent mechanisms (4). Autoantibodies contribute to autoimmunity by different mechanisms, including immune complex (IC)-mediated and antibody-dependent cell-mediated cytotoxicity (ADCC) hypersensitivity reactions, and by instructing innate immune cells to produce pathogenic cytokines, such as interferon (INF)-α, tumor necrosis factor (TNF) and interleukin (IL)-1 (5). Suggested autoantibody-independent functions include antigen presentation, T cell activation and polarization towards T-helper (Th)2, and dendritic cell (DC) modulation. These functions are mediated by immunoregulatory cytokines, chemokines, as well as growth factors (5).

As we described, these autoantibodies can form ICs, activate the complement cascade, recruit other inflammatory cells, and subsequently these processes result in tissue damage. Due to the impaired clearance of ICs and apoptotic material, autoantigens are presented to T cells by professional APCs, including monocytes, macrophages, plasmocytoid dendritic cells (pDCs) and even B cells, which further induces T cell activation (6-10). Such activated T cells stimulate antigen specific B lymphocytes. These processes require sufficient interaction between co-stimulatory molecular pairs. In physiological circumstances, the expansion of autoreactive B cells can be suppressed by regulative mechanisms, however in lupus reduced number and impaired function of regulative T cells were describe by others and also by us (11-13).

These molecular findings clearly gave rationale for B cell modulating therapies in lupus patients. New agents that directly target abnormal B lymphocytes in SLE include B-cell depleting or modulating monoclonal antibodies (mAb) such as anti-CD20, Rituximab (chimeric mouse anti-human CD20 mAb) and its modified version Ocrelizumab (fully human mAb against CD20), or those blocking inhibitory cell surface molecule CD22, a glycoprotein present on mature B-cells (i.e. Epratuzumab), or further the DNA-specific B cell tolerogen LJP394 (Abetimus), an oligonucleotide-based investigational drug designed to treat patients with lupus nephritis by specifically reducing anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody levels (14,15). The member of the TNF-superfamily, B cell activating factor/B lymphocyte stimulator (BAFF/BLyS) plays a crucial role in the development, maturation and proliferation of B-cells. Increased BAFF/BLyS production leads to excess B-cell survival catalyzed by the induction of anti-apoptotic pathways and the escape of autoreactive B-cells from negative selection, and could therefore initiate pathological autoimmune processes (16).

Transgenic (Tg) mice overexpressing BAFF/BLyS develop an autoimmune disorder similar to SLE and show impaired B cell tolerance and altered T cell differentiation (17). In accordance with these findings, serum levels of BAFF/BlyS have been shown to be significantly higher in patients with lupus, compared to healthy individuals, suggesting an important role for the molecule in the disease pathogenesis (18).

The association of BAFF/BLyS with autoimmune diseases, including SLE has lead to widespread efforts from the pharmaceutical industry to develop agents that neutralize BAFF/BLyS. The administration of the decoy receptor for BAFF/BLyS /transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI-Ig)/ has been tested in a phase-I trial with healthy volunteers, and a human monoclonal antibody specific for BAFF (LymphoStat-B, belimumab) is also currently in clinical trials with SLE patients (19). In clinical trials LymphoStat-B was well tolerated in the treatment of SLE for over 3 years. Belimumab treatment significantly reduced symptoms of SLE, and decreased anti-dsDNA and antinuclear antibody titers (20).

3. MODIFICATION OF CO-STIMULATORY PATHWAYS

Second signal is an elementary requirement for the activation of T, as well as B cells, and even such molecular pairs must anchor B and T cells to each other for effective T cell helper function. T cell cytokines affect B cells by stimulating cell division, isotype switching, and increasing antibody avidity. The other drug-development approach can be to block co-stimulatory interactions between T and B cells, e.g. by inhibiting the CD40-CD40L pathway with monoclonal Ab (21-24). CD40 is expressed on APCs and its ligand CD154, which is transiently expressed on activated T cells. Interactions between CD40 and CD40L have been shown to facilitate T-cell-dependent immune responses and to play a pivotal role in major histocompatibility complex (MHC) molecule expression, cytokine release, phagocytosis and antigen presentation (25-27). MAbs have been developed against CD40L with variable responses in human lupus. Preliminary results showed possible efficacy but not safety as thromboembolic complications occurred with high frequency (28-29).

Abatacept (Orencia) is a receptor fusion protein of cytotoxic T lymphocyte antigen 4 (CTLA4) and Ig that prevents binding of CD80 (B7) to CD28. In murine lupus there are promising results indicating reversal of proteinuria and improved survival. Abatacept effectively prevents SLE onset in several murine models and, when used in combination with cyclophosphamide, could induce remission of active SLE nephritis (30).

Table 1. Major novel molecular targets in SLE

Target/name	Description/Function
CD20 Rituximab Ocrelizumab	Mouse-human chimeric monoclonal antibody against CD20, an integral membrane protein that is expressed from early pre-B cell stage and is maintained through mature B cell development. Its function is believed to be cell cycle initiation and cell differentiation. Promising clinical efficacy and favorable safety profile has been reported based on available trial results.
CD22 Epratuzumab	Glyocoprotein that is a B-lymphocyte-restricted member of the immunoglobulin superfamily, and a member of adhesion molecules. It negatively regulates B cell activation and several intracellular pathways.
BAFF/BLyS Belimumab	Member of TNF ligand superfamily. BAFF/BLyS binds to surface receptors on activated B cells and subsequently induces B cell proliferation, survival and differentiation to plasma cells. Serum BAFF/BLyS is increased in human lupus. There are few ongoing studies assessing the efficacy and safety of anti-BAFF/BLyS MAb-s or soluble receptors.
LJP 394 Abetimus	Composed of 4 identical strands of dsDNA that are covalently linked to an ethylenglycol backbone. The supposed mechanism of action is the formation and rapid clearance of DNA-aDNA complexes as well as tolerizing B cells by anergy. According to study observations it reduced the level of aDNA but did not prolonged time to renal flare.

4. ANTI-CYTOKINE THERAPY, SOLUBLE MEDIATORS

Type I interferon pathway is another key step in the pathogenesis of SLE by promoting DC maturation, T cell survival and autoantibody production (31). Onset of SLE has been reported during recombinant (r)INF I therapy of patients with hepatitis or neoplasms (32-34). Almost all nucleated cells are capable of producing IFN I, pDCs are the most potent in this respect (35). PDCs can be activated through toll-like receptors (TLR), especially TLR 7/8 and 9, by DNA and RNA derived from pathogens as well as from endogen sources. Upon activation these cells migrate to lymph nodes, furthermore they are present in inflamed skin and kidney in patients with lupus. Elevated serum IFN alpha and IFN-stimulated gene-expression are found in about 2/3 of SLE patients (36,37). This IFN signature has been proven as clinically important correlating with disease activity and renal as well as central nervous system (CNS) involvement (38). Genetic abnormalities resulting in increased IFN-I production or signaling are associated with SLE. On the other hand, DCs producing type I interferons, which are critically involved in the pathogenesis of SLE. Not only pathogen associated molecular patterns (PAMPs), but also endogenous RNA and DNA, especially those containing CpG motives may activate pDCs.

Targeting different points of the type I IFN pathway may be beneficial therapeutically. INF-I, interferon receptors and IFN-producing cells as well as IFN –inducers and molecules of the IFN-I signaling pathway may serve as potential therapeutic targets. Several of them have already shown promising effects in animal studies and clinical trials also may begin in the near future (39,40).

Soluble mediators, such as cytokines, Ig receptors, and the complement system can be targets for lupus therapy. Among cytokines, IL-1, IL-10 and IL-6 as well as IL-18 seem to be promising targets (41,42). The utilization of anti-TNF therapies in lupus are somewhat controversial, as these products may induce antinuclear, anti-dsDNA, as well as anti-cardiolipin antibodies, potentially further propagating the harmful autoimmune machinery in lupus (43-45).

The complement system is composed of a complex cascade of activating and regulative proteins. Its activation promotes chemotaxis of inflammatory cells and enhances phagocytosis by neutrophils and monocytes, and as such initiates inflammation and tissue injury. Activation of the complement system may be induced by classical, alternative and mannose-binding lectin (MBL) pathways. Complement factors and complement receptors are required for sufficient clearance of cell debris and ICs (46). Numerical and functional defects of the complement receptor 1 (CR1) have been described and was also the focus of our research interest. Taking together the beneficial and harmful roles of complement in the pathogenesis of SLE, there are several hypothetic possibilities to modulate this system therapeutically (47,48).

SLE is characterized by excessive IC formation and defective clearance by the mononuclear phagocyte system (49-52). Handling of ICs by mononuclear phagocyte system (MPS) mostly depends on the function Fcγ receptors, which can be divided to two general classes: stimulatory and inhibitory. Therapeutic interventions altering this balance may minimize Fcγ R-mediated tissue damage, maintain tolerance, and influence antibody repertoire (53,54). Besides many others, this is one way of action for high dose intra-venous immunoglobulin (IVIG) therapy (53).

Signaling through the T cell receptor (TCR) leads to the activation of many genes. T cells have persistently hyperpolarized mitochondria, high levels of reactive oxygen species and low level of Adenosine-5'-triphosphate (ATP), which decreases activation-induced apoptosis, predisposes for necrosis, thus stimulating inflammation is SLE (55). T cells can also be tolerized by hCDR1 (Edratide), a peptide synthesized on the basis of the sequence of the first complementarity-determining region (CDR1) of an autoantibody, derived from the variable heavy chain (VH) region of the immunoglobulin (Ig) in human antibody to dsDNA. Treatment with edratide ameliorates disease symptoms in lupus mouse models (56), moreover it may induce regulative T cells.

5. $CD34^+$ STEM-CELL THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Most lupus patients with progressive disease with a predominant nephropathy, pulmonological, bone marrow or nervous system involvement, non-responders for conventional immune-modulatory treatment are excellent candidates for stem-cell therapy. As part of the conditioning treatments, authors from the National Cancer Institute in Bethesda have recently reported the benefit of adding fludarabine and rituximab (anti-CD20 monoclonal

Table 2. Potential side effects and clinical trials of novel molecular targets in SLE

	Potential side effects	Study References
Rituximab	• Infusion reactions • Cardiac arrest • Tumor lysis syndrome, causing acute renal failure • Infections • -hepatitis b reactivation • -other viral infections (e.g. Latent jc virus) • -progressive multifocal leukoencephalopathy (pml) • Immune toxicity • Pulmonary toxicity	65
Ocrelizumab	• Infusion reactions • Diarrhea • Ophthalmic herpes zoster • Malignancies • Upper respiratory tract, urinary tract, and viral infections	66
Epratuzumab	• Infusion reactions • Upper respiratory tract infection • Anemia and fatigue • Arthralgia, • Abdominal and chest pain • Oral candidiasis • Peripheral edema • Rash	67
Belimumab	• Infusion reactions • Arthralgia • Rash • Diarrhea • Joint swelling • Synovitis • Depression • Upper respiratory tract infection • Thrombocytopenia • Neutropenia • Pancreatitis • Cellulitis staphylococcal • Sepsis • Aspartate aminotransferase increased • Blood creatinine increased • Dehydration • Pain in extremity • Peripheral edema	19,68
Abetimus	• Infusion reactions • Chest and neck pain • Facial edema • Hemorrhage • Dyspepsia • Gingivitis • Gastrointestinal distress • Anemia • Ecchymosis • Leukopenia • Hypokalemia • Dehydration • Musculoskeletal • Paresthesia • Depression • Vertigo • Anxiety • Upper respiratory tract infections • Skin infections, rash • Urogenital infection	69,70

antibody) to the conventional protocol (57). Autologous stem cell transplantation (ASCT) was beneficial and a significant clinical improvement was observed in most of the patients at the early post-transplant period. The mean systemic lupus erythematosus disease activity index (SLEDAI) scores fell from 33.2 before, to a mean of 2.6-3.8 after transplant. Antinuclear antibodies, as well as anti-dsDNA antibody titers became negative in 80% of the patients after therapy. However, these abnormalities reappeared in about 25% of the patients subsequently. Concomitant steroid therapy could be discontinued for good in almost half of the cases, and sustained improvement could be observed in more than 50% of the patients, after a median follow-up of 3 years. According to data from the Northwestern University, the probability of overall and disease-free survivals was 85% and 50% at 5

years, respectively (58). Pilot studies on lupus patients underlined the fact that the $CD34^+$ ASCT is a beneficial therapy in the disease, yet further, more extensive, randomized studies are needed to clarify the exact role of this intervention in the treatment for SLE (59-63).

Interestingly, high-dose cyclophosphamide (HDC), without stem cell transplantation has been described to lead to rapid hematopoietic reconstitution and has significant clinical benefit in patients with refractory SLE (64). The treatment regime was: 50 mg/kg of cyclophosphamide for 4 consecutive days followed by 5 μg/kg granulocyte colony-stimulating factor (GCSF) for 2 consecutive days. HDC, the foundation of virtually all conditioning regimens for ASCT, is not myeloablative; therefore, when HDC is used alone, autografting, with its potential for reinfusing autoreactive effector cells, is not required (64).

6. SIDE EFFECTS

Although the safety profile of these innovative approaches are much better, than those of traditional immune suppressive drugs, they can only cautiously been used as severe and sometimes fatal adverse events have also been reported. The ongoing clinical trials with novel therapies in SLE, as well as potential side effects are summarized in Table 2. Therefore, double-blind, multi-centre, randomized, placebo-controlled studies are needed to find those effective and safe compounds that can be introduced into daily practice.

In the pathogenesis of systemic lupus erythematosus the intricate interaction of numerous inflammatory mediators, signalization molecules enables us to see a future, where individually-tailored therapies could be designed for patients, leading them to a better quality of life in this potentially fatal, systemic autoimmune disease.

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Abbreviations: ATP: adenosine-5'-triphosphate, ADCC: antibody-dependent cell-mediated cytotoxicity, APCs: antigen-presenting cells, ASCT: autologous stem cell transplantation, BAFF/BLyS: B cell activating factor/B lymphocyte stimulator, CNS: central nervous system, CDR1: complementarity-determining region, CR1: complement receptor 1, CTLA4: cytotoxic T lymphocyte antigen 4, DC: dendritic cell, dsDNA: double-stranded deoxyribonucleic acid, HDC: high-dose cyclophosphamide, Ig: immunoglobuline, GCSF: granulocyte colony-stimulating factor, IC: immune complex, INF-α: interferon-alpha, IL-1: interleukin-1, IVIG: intra-venous immunoglobulin, JCV: John Cunningham virus, MHC: major histocompatibility complex, MBL: mannose-binding lectin, mAb: monoclonal antibody, MPS: mononuclear phagocyte system, PAMP: pathogen associated molecular pattern, pDC: plasmocytoid dendritic cell, PML: progressive multifocal leukoencephalopathy, rINF I: recombinant interferon I, SLE: systemic lupus erythematosus, SLEDAI: systemic lupus erythematosus disease activity index, TCR: T cell receptor, Th2: T-helper type 2, TLR: toll-like receptor, Tg: transgenic, TACI: transmembrane activator and calcium modulator and cyclophilin ligand interactor, TNF: tumor necrosis factor, VH: variable heavy chain

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