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B-CELL-TARGETED THERAPIES IN THE TREATMENT OF AUTOIMMUNE SKIN DISEASES – A COMPREHENSIVE REVIEW OF MECHANISMS, EFFICACY, AND FUTURE DIRECTIONS

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ABSTRACT

Autoimmune skin diseases (AISDs) constitute a complex group of conditions whose pathogenesis is based on abnormal activation of the immune system, leading to the production of autoantibodies and damage to skin structures. In recent years, a key role in these processes has been attributed to B lymphocytes, which not only produce autoantibodies but also perform regulatory and effector functions in the immune response. The development of biological therapies targeting B lymphocytes has revolutionized the treatment of many diseases, particularly pemphigus, where anti-CD20 antibodies have become the standard of care.

The aim of this article is to provide a comprehensive overview of the role of B lymphocytes in the pathogenesis of AISD, an overview of available targeted therapies (including monoclonal antibodies, kinase inhibitors, and plasma cell-targeted therapies), and an analysis of their efficacy, safety, and limitations. Attention was paid to new therapeutic strategies that may enable more selective and sustained modulation of the immune response.

KEYWORDS

Autoimmunity, Cellular Immunotherapy, Chimeric Antigen Receptor T Cells, Autoimmune Skin Diseases (AISDs), B Lymphocytes, Anti-CD20 Antibodies, Pemphigus, Pemphigoid, Cutaneous Lupus Erythematosus, Scleroderma

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1. Introduction

Autoimmune skin diseases encompass a wide spectrum of conditions, such as pemphigus, pemphigoid, cutaneous lupus erythematosus, scleroderma, and dermatomyositis. The common denominator of these conditions is the presence of autoreactive immune mechanisms leading to chronic inflammation and tissue damage.

For many years, the mainstay of treatment was non-selective immunosuppressive methods, including glucocorticosteroids and classic immunosuppressive drugs. Although effective in controlling symptoms, these therapies are associated with numerous side effects, such as infections, osteoporosis, diabetes, and secondary cancers.

Advances in molecular immunology have allowed the identification of key elements of pathogenesis, including the central role of B lymphocytes. Consequently, targeted therapies have been developed, enabling more precise intervention in the immune system.

1.2 Materials and Methods

A literature review was conducted in PubMed, Web of Science, Scopus, and Google Scholar. Search terms included combinations of the words "B lymphocytes," "pemphigus," "autoimmune skin diseases," "systemic sclerosis," "pemphigoid," "anti-CD-20 antibodies," "anti-BAFF therapies," "Bruton's kinase (BTK) inhibitors," and "CAR-T cell therapies." This review included publications in English published between 2006 and 2025, observational studies, case reports, meta-analyses, literature reviews, reports, and publications from healthcare institutions. Articles deemed unreliable, irrelevant, or of low methodological quality were excluded. Selected publications were analyzed qualitatively and thematically to provide a multidimensional perspective on B cell-targeted therapy for autoimmune skin diseases.

2. B Lymphocyte Biology and Their Role in Autoimmunity

2.1 B Lymphocyte Development and Differentiation

B lymphocytes, which originate in the bone marrow from hematopoietic stem cells, constitute a fundamental element of the humoral immune system. Their primary function is antibody production, but it is now known that they also participate in antigen presentation, regulation of the immune response, and activation of other immune cells. In autoimmune skin diseases, B lymphocytes play a crucial role in both the initiation and maintenance of the chronic autoimmune response [1].

B lymphocyte development begins in the bone marrow, where subsequent cell stages mature pro-B cells, pre-B cells, and immature B lymphocytes. During this process, immunoglobulin gene rearrangement and the selection of autoreactive clones occur. Central tolerance mechanisms aim to eliminate or inactivate lymphocytes that recognize self-antigens. Disruption of these mechanisms leads to the survival of autoreactive B lymphocytes, which is one of the fundamental steps in the development of autoimmunity [2]. Mature, naive B lymphocytes leave the bone marrow and migrate to peripheral lymphoid organs such as the spleen and lymph nodes, where they can become activated upon contact with antigen. B cell activation occurs primarily through the BCR (B-cell receptor), which recognizes specific antigens. However, full activation also requires interaction with CD4⁺ T helper cells and the presence of costimulatory signals, particularly the CD40-CD40L interaction [3].

Key steps in B cell differentiation include:

- activation via the BCR,
- interaction with T helper cells,
- antibody proliferation and affinity maturation,
- immunoglobulin class switching,
- formation of memory B cells and plasma cells. In the germinal centers, activated B lymphocytes

undergo somatic hypermutation and clonal selection, leading to the production of antibodies with high affinity for the antigen. In autoimmune diseases, the mechanisms controlling this process may be impaired, resulting in the production of autoantibodies with high pathogenic activity [4].

Plasma cells formed through B lymphocyte differentiation are responsible for the production of autoantibodies directed against skin structures, such as desmogleins in pemphigus or hemidesmosome proteins in bullous pemphigoid. Memory B cells, on the other hand, can persist for long periods and are responsible for disease relapses after periods of remission [5].

Also important in autoimmune skin diseases are impaired peripheral tolerance and impaired cooperation between B and T lymphocytes. Excessive B lymphocyte activation leads to chronic inflammation, a sustained autoimmune response, and tissue damage [6].

2.2 Mechanisms of Autoreactivity

In autoimmune skin diseases (AISD), such as pemphigus vulgaris and bullous pemphigoid, a key role is played by the loss of immunological tolerance to self-antigens. Autoantigens are primarily proteins responsible for the integrity and adhesion of epidermal cells and the dermal-epidermal junction. In pemphigus, the main autoantigens are desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3), members of the desmosomal cadherin family. These proteins are responsible for the proper connections between keratinocytes and the maintenance of epidermal cohesion. In bullous pemphigoid, however, autoantibodies are primarily directed against hemidesmosome proteins—BP180 (collagen XVII) and BP230—which stabilize the junction of the epidermis with the basement membrane [5]. Recognition of these autoantigens by the immune system leads to the activation of a humoral response and the production of IgG autoantibodies. In pemphigus, anti-desmoglein antibodies cause a loss of adhesion between keratinocytes (acantholysis), resulting in the formation of intraepidermal blisters. In pemphigoid, complement activation and the influx of inflammatory cells lead to damage to the dermal-epidermal junction and the formation of subepidermal blisters [5]. A key step in the initiation of an autoimmune response is the presentation of autoantigens by antigen-presenting cells (APCs). In the skin, this function is primarily performed by dendritic cells, including Langerhans cells, as well as macrophages and activated B lymphocytes. The process begins with the uptake of autoantigen, its degradation into short peptides, and its presentation in a complex with major histocompatibility complex class II (MHC II) molecules. CD4⁺ T lymphocytes are then activated, stimulating B lymphocytes to proliferate, mature, and produce autoantibodies [3].

The genetically determined ability to present autoantigens plays a significant role in the pathogenesis of AISD. A strong association between pemphigus and specific HLA class II alleles has been demonstrated, particularly HLA-DRB104:02 and HLA-DQB105:03. These molecules exhibit high affinity for desmoglein 3 epitopes, which promotes the activation of autoreactive T helper lymphocytes and the development of an autoimmune response. The presence of these alleles is one of the most important genetic predisposition factors for the disease [3].

B lymphocyte autoreactivity may result from impaired immune tolerance mechanisms at both the central and peripheral levels. Under physiological conditions, autoreactive B clones are eliminated or inactivated during maturation in the bone marrow. In autoimmune diseases, this process is insufficient, allowing the survival of cells capable of recognizing self-antigens. Furthermore, chronic stimulation with proinflammatory cytokines, particularly BAFF (B-cell activating factor), increases the survival of autoreactive B lymphocytes and increases the production of autoantibodies. Also important is the dysfunction of regulatory T lymphocytes (Treg), which normally inhibit excessive activation of the immune response [4].

Consequently, a chronic inflammatory process persists, and autoantibodies directed against structural skin proteins are continuously produced. These mechanisms are responsible for both the development of skin lesions and the chronic, recurrent nature of autoimmune skin diseases.

2.3 Effector Functions of B Lymphocytes

For a long time, B lymphocytes were viewed almost exclusively as cells responsible for antibody synthesis. However, contemporary immunodermatology reveals a much broader picture. In autoimmune skin diseases, B lymphocytes perform numerous effector functions that go beyond classical immunoglobulin production and include active modulation of the immune response at the cellular, tissue, and molecular levels [7]. In diseases such as pemphigus, bullous pemphigoid, cutaneous lupus erythematosus, dermatomyositis, and systemic sclerosis, B lymphocytes participate in the initiation, amplification, and maintenance of the chronic inflammatory process [5]. Their effector functions can be divided into several fundamental mechanisms: autoantibody production antigen presentation cytokine secretion organization of the inflammatory microenvironment co-regulation of T lymphocyte responses participation in tissue remodeling formation of autoimmune memory [8]

2.3 Effector Functions of B Lymphocytes in Autoimmune Skin Diseases

2.3.1 Autoantibody Production

The most classic effector function of B lymphocytes is their differentiation into plasma cells and the production of immunoglobulins. Under physiological conditions, antibodies participate in the elimination of pathogens through their neutralization, opsonization, and complement activation. However, in autoimmune skin diseases, tolerance to self-antigens is lost and autoantibodies directed against skin structures are produced [5].

In pemphigus vulgaris, IgG autoantibodies, primarily IgG4, are directed against desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3), components of keratinocyte desmosomes. Binding of autoantibodies to desmogleins leads to impaired intercellular adhesion and acantholysis, resulting in the formation of intraepidermal blisters [5]. In bullous pemphigoid, antibodies are primarily directed against BP180 (collagen XVII) and BP230—hemidesmosome proteins responsible for the stability of the dermal-epidermal junction [9].

The pathogenic effect of autoantibodies is not limited to direct antigen binding. Secondary mechanisms also play a significant role, such as:

- activation of the complement system,
- recruitment of inflammatory cells,
- release of proteases and reactive oxygen species,
- induction of skin cell apoptosis.

Complement activation leads to the production of proinflammatory mediators, particularly C3a and C5a, which enhance chemotaxis of neutrophils and eosinophils. These cells release proteolytic enzymes, causing damage to intercellular junctions and the skin's basement membrane [9]. In bullous pemphigoid, this process plays a particularly important role in the development of subepidermal blisters. Long-lived plasma cells can maintain autoantibody production for many months or years, even despite immunosuppressive treatment. This phenomenon partially explains the chronic and recurrent nature of autoimmune skin diseases [10].

2.3.2 Antigen Presentation

In addition to antibody production, B lymphocytes function as professional antigen-presenting cells (APCs). Thanks to the presence of the BCR receptor, they can capture even small amounts of specific autoantigens, process them, and present them to CD4⁺ T lymphocytes in the context of MHC class II molecules [3].

Different autoantigens are presented in different autoimmune skin diseases:

- in pemphigus—fragments of desmoglein 3 and desmoglein 1;
- in bullous pemphigoid—NC16A domains of the BP180 protein;
- in lupus erythematosus—nuclear nucleoproteins, DNA, and nucleosome complexes [3].

Autoantigen presentation leads to the activation of autoreactive T helper cells. Activated T cells secrete cytokines such as IL-21, IL-4, and IFN- γ , which enhance the proliferation, maturation, and differentiation of B cells [11]. IL-21 plays a particularly important role in the formation of plasma cells and the maintenance of germinal centers, while IL-4 promotes antibody class switching toward IgG4, which is dominant in pemphigus [11]. As a result, a pathological positive feedback loop is created between T and B cells. B cells activate T cells through antigen presentation, and T cells enhance B cell activation and autoantibody production. This mechanism is responsible for maintaining a chronic autoimmune response [12].

2.3.3 Cytokine Production

B lymphocytes also function as immunoregulatory cells by secreting numerous cytokines that influence the inflammatory environment of the skin. They can produce both proinflammatory and anti-inflammatory cytokines, regulating the immune response [6].

One of the most important cytokines produced by B lymphocytes is interleukin 6 (IL-6). This cytokine:

- stimulates the differentiation of Th17 lymphocytes,
- increases antibody production,
- activates the acute phase response,
- increases the survival of autoreactive B lymphocytes.
- High IL-6 concentrations are observed in conditions such as:
- systemic lupus erythematosus,
- systemic sclerosis,
- dermatomyositis [6].

IL-6 contributes to the severity of chronic skin inflammation, increased inflammatory cell infiltration, and progression of tissue damage. TNF- α (tumor necrosis factor alpha) also plays an important role, as it:

- activates endothelial cells,
- increases vascular permeability,
- increases the expression of adhesion molecules,
- stimulates the recruitment of leukocytes to the skin [13].

Consequently, TNF- α is responsible for the development of erythema, edema, and inflammatory infiltrate characteristic of active skin lesions. Excessive TNF- α production also contributes to tissue destruction and the perpetuation of chronic inflammation. In addition to proinflammatory cytokines, some B lymphocytes can secrete IL-10 and perform a regulatory function (Breg), inhibiting excessive activation of the immune system. However, in autoimmune diseases, the number and function of Breg cells can be impaired, further contributing to the persistence of the autoimmune response [7].

3. Pathogenesis of Selected B-Cell-Dependent Skin Diseases

3.1 Pemphigus

Pemphigus is an acantholytic bullous disease of the mucous membranes and/or skin, caused by the presence of pathogenic autoantibodies in the circulation and bound in vivo in the intercellular spaces of the epidermis, which are directed against various desmosome adhesion molecules. The clinical presentation and course of individual types of pemphigus depend on the type of antigen recognized by the autoantibodies and the stage of the disease process [14].

Pemphigus vulgaris (PV) most often begins insidiously, with painless erosions on the buccal mucosa, soft and hard palate, and/or erosive gingivitis. Initially mildly uncomfortable, the erosions eventually become painful and impede feeding. Less frequently, the onset is sudden. Erosions can involve the larynx, esophagus, conjunctiva, genital area, and anus [15,16].

Pemphigus vegetans is a very rare variant of bulla vulgaris, clinically characterized by the presence of verrucous, verrucous, and pustular lesions. In the Neumann variant, verrucous lesions are seen around the mouth, while in the Hallopeau variant, pustular and verrucous lesions occur in the axillae and inguinal folds [15,16].

Pemphigus foliaceus, seborrheic, and erythematous

Skin lesions characterized by blisters with a loose cover that rapidly rupture spontaneously, in pemphigus foliaceus, seborrheic, and erythematous (PF), which develop into honey-yellow crusts. Lesions are located on the upper chest and back, particularly in the seborrheic areas, as well as on the face and scalp. In untreated cases, erythroderma may develop. The mucous membranes are free [15,16].

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP/PAMS) coexists with malignancies, most commonly lymphoreticular hyperplasias such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, as well as thymoma and Castleman's tumor. In one-third of patients, pemphigus is detected before the cancer is diagnosed, especially since the symptoms of PNP/PAMS may precede the malignancy. Clinically, this type of pemphigus is characterized by a marked predilection for mucosal involvement. Initially, cheilitis occurs, often hemorrhagic, ulcerative stomatitis, with painful erosions leading to swallowing difficulties. Oral lesions are accompanied by cicatricial conjunctivitis and keratitis, as well as erosions of the genital mucosa. In some patients, erosions develop in the throat, nose, and esophagus, causing pain on swallowing and reflux.

Skin lesions are multiform, ranging from lichen planus-like lesions to graft-versus-host disease (GVHD) lesions. They may also resemble erythema multiforme or pemphigoid, and most commonly pemphigus vulgaris. Skin and mucosal lesions may be accompanied by life-threatening pulmonary lesions characterized by alveolitis and/or obstructive bronchitis (bronchiolitis obliterans), which is a poor prognostic symptom [15,16].

IgA Pemphigus

Two variants of IgA-mediated pemphigus are known: subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic type (IEN). Skin lesions present as pustules on an erythematous base in SPD and pustules with an annular pattern on the trunk in IEN [16].

3.2 Pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease, characterized by the formation of subepidermal blisters and chronic skin inflammation. The disease's pathogenesis is primarily associated with the presence of autoantibodies directed against hemidesmosome proteins—BP180 (collagen XVII) and BP230. These proteins are responsible for the stability of the dermal-epidermal junction and the maintenance of basement membrane integrity [5]. IgG autoantibodies bind to basement membrane antigens, leading to complement activation and the initiation of an inflammatory response. Activation of C3a and C5a components is particularly important, as they have a chemotactic effect on inflammatory cells, particularly eosinophils and neutrophils [9]. Eosinophilic infiltration is one of the characteristic histopathological features of bullous pemphigoid. Eosinophils release proteolytic enzymes, metalloproteinases, and reactive oxygen species, which lead to the degradation of basement membrane structures and separation of the epidermis from the dermis [17].

Unlike pemphigus, in which the dominant mechanism is direct disruption of adhesion between keratinocytes, complement- and effector-cell-mediated inflammation plays a more significant role in pemphigoid. However, the role of B lymphocytes is also crucial, as they are responsible for the production of autoantibodies and the presentation of autoantigens to T helper lymphocytes [18].

In pemphigoid, CD4⁺ T lymphocytes are activated, particularly the Th2 response. Cytokines such as IL-4, IL-5, and IL-13 enhance the production of autoantibodies and the activation of eosinophils [19]. IL-5 plays a significant role in the maturation and survival of eosinophils, which explains their numerous infiltrates in skin lesions. Autoimmune bullous diseases can be divided into:

- diseases associated with antibodies against desmosomal proteins (the pemphigus group),
- diseases associated with antibodies against hemidesmosomal proteins (autoimmune subepidermal bullous diseases).

Both groups of diseases lead to loss of skin integrity, but differ in the location of damage, the nature of the inflammatory infiltrate, and the immunological mechanisms involved [25].

3.3 Lupus erythematosus

Lupus erythematosus is a chronic, multisystem autoimmune disease in which impaired humoral response and excessive immune activation play a significant role. B lymphocytes, which produce autoantibodies against nuclear and cytoplasmic antigens, play a key role in the disease pathogenesis [20].

The most important autoantibodies found in lupus include:

- anti-double-stranded DNA (dsDNA) antibodies,
- anti-Ro/SSA antibodies,
- anti-La/SSB antibodies,
- anti-Sm antibodies,
- anti-nucleosome antibodies [20].

Autoantibodies form immune complexes that accumulate in the skin, vessels, and other tissues. These complexes activate the complement system, leading to chronic inflammation and tissue damage [21]. In the skin, this results in keratinocyte damage, inflammatory infiltration, and the development of characteristic skin lesions, such as erythema, photosensitivity, and scarring.

One of the most important immunopathological mechanisms in lupus is excessive activation of the type I interferon pathway, referred to as the "interferon signature." Immune complexes containing nucleic acids are captured by plasmacytoid dendritic cells (pDCs), which produce large amounts of interferon α (IFN- α) [22]. This cytokine:

- increases B lymphocyte activation,
- increases antigen presentation,
- stimulates autoantibody production,
- maintains the chronic autoimmune process.

Type I interferon also influences increased keratinocyte apoptosis and the expression of nuclear autoantigens, further intensifying the autoimmune response [23]. B lymphocytes in lupus fulfill both effector and regulatory functions. On the one hand, they produce autoantibodies and proinflammatory cytokines, while on the other, a subpopulation of regulatory B lymphocytes (Breg) can secrete IL-10 and limit an excessive immune response. In active lupus, Breg cell function is often impaired, which contributes to the persistence of inflammation [7]. BAFF (B-cell activating factor) also plays a significant role in the survival of autoreactive B lymphocytes. Elevated BAFF levels are observed in patients with lupus and correlate with disease activity [24]. This cytokine increases the survival of autoreactive B lymphocytes and promotes the differentiation of autoantibody-producing plasma cells.

4. B-Cell Targeted Therapies

4.1 Anti-CD20 Antibodies

Biological therapy targeting the CD20 antigen is one of the most important achievements in modern immunodermatology, and its use in the treatment of autoimmune skin diseases such as pemphigus and bullous pemphigoid has led to a significant shift in therapeutic approaches and a significant improvement in patient prognosis [25,26]. The mechanism of action of this therapy is complex and involves several processes occurring at the molecular, cellular, and tissue levels, which together lead to profound modulation of the pathological immune response.

The target for anti-CD20 antibodies, such as rituximab, is the CD20 antigen, a surface protein present on pre-B lymphocytes and mature B lymphocytes but absent on stem cells and plasma cells [25-27]. This specific expression is crucial for the safety and efficacy of the therapy, as it enables the selective elimination of the B lymphocyte population responsible for initiating and sustaining the autoimmune response, while simultaneously preserving the ability to regenerate the B cell system from hematopoietic precursors [27].

After binding the anti-CD20 antibody to the B lymphocyte surface, its elimination occurs through several parallel effector mechanisms. One of the most important is antibody-dependent cellular cytotoxicity (ADCC), in which the Fc fragment of the immunoglobulin interacts with Fc γ receptors present on effector cells such as NK cells and macrophages [28]. This interaction leads to the release of cytotoxic mediators, including perforins and granzymes, which induce target cell lysis. Concurrently, complement-dependent cytotoxicity (CDC) is activated, which involves initiation of the classical complement activation pathway through the binding of C1q to the antibody-antigen complex [29]. This cascade results in the formation of a complex that attacks the cell membrane, resulting in membrane damage and cell death. Furthermore,

opsonization of B lymphocytes by antibodies enables their recognition and phagocytosis by macrophages, which constitutes another important elimination mechanism [30]. Direct induction of apoptosis resulting from disruption of intracellular signaling following CD20 binding, including changes in calcium homeostasis and activation of proapoptotic pathways [31], is also significant.

The result of these processes is a rapid and profound depletion of B lymphocytes in both the circulation and lymphatic organs, persisting for many months [28]. In the context of autoimmune skin diseases, this is of fundamental importance, as B lymphocytes play a central role in the pathogenesis of these conditions, primarily through the production of autoantibodies [43]. In pemphigus, autoantibodies directed against desmogleins disrupt adhesion between keratinocytes, leading to acantholysis and blistering, whereas in pemphigoid, antibodies against basement membrane proteins activate complement and induce an inflammatory reaction resulting in separation of the epidermis from the dermis [5,26]. B-cell depletion leads to an interruption of this process by eliminating precursor cells for plasma cells, which in turn causes a gradual decrease in autoantibody levels [32].

A significant aspect of anti-CD20 therapy is that, despite the lack of direct effect on long-lived plasma cells, a significant decrease in autoantibody levels is observed over time [33]. This is due to the inhibition of new plasma cell formation and the reduction of activation of existing ones through the elimination of stimulatory signals from B and T lymphocytes [34]. Furthermore, studies indicate that the reduction affects autoantibodies more than protective antibodies, suggesting the relative selectivity of this therapy towards pathological B lymphocyte clones [34]. Another key mechanism of action of anti-CD20 therapy is its influence on the cellular response, particularly on T lymphocytes. B lymphocytes play an important role as antigen-presenting cells, enabling the activation of CD4⁺ T lymphocytes through the presentation of autoantigens in the context of MHC class II molecules [35]. Elimination of B lymphocytes leads to a significant reduction in this function, which results in reduced activation of autoreactive T lymphocytes. Studies have shown that rituximab therapy reduces the number of T lymphocytes specific for skin autoantigens, while maintaining the immune response to non-self-antigens [36]. This indicates selective silencing of the autoimmune response without global immunosuppression.

Another important element of anti-CD20 therapy is its impact on the inflammatory environment in the skin. Reducing the number of B lymphocytes leads to a reduction in the production of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), which translates into reduced activation of effector cells and a reduced inflammatory infiltrate [36,49]. In diseases such as bullous pemphigoid, reducing the recruitment of eosinophils and neutrophils is particularly important, as they play a key role in tissue damage through the release of proteases and reactive oxygen species [9,19]. Furthermore, this therapy limits the formation of ectopic lymphoid structures in the skin, which, under conditions of chronic inflammation, can serve as local sites for autoantibody production [6]. One of the most interesting aspects of anti-CD20 therapy is the phenomenon known as "immune reset." After a period of B cell depletion, their gradual regeneration from progenitor cells in the bone marrow occurs [61,62]. The newly formed B lymphocytes are characterized by a more naive phenotype and a reduced propensity for autoreactivity, suggesting the restoration of more normal immunological tolerance [2]. This process may explain the long-term remissions observed in patients, even after a single course of treatment [25].

Despite its high efficacy, anti-CD20 therapy is not without its limitations. The most important of these is the lack of direct effect on long-lived plasma cells, which may continue to produce autoantibodies, which in some cases leads to disease relapses [10]. Furthermore, after B cell regeneration, autoreactive clones may reappear, especially under conditions of sustained immune stimulation [2]. Furthermore, BAFF levels are observed to increase following B cell depletion, which may promote the survival of new B cells, including potentially autoreactive ones [97,98]. In summary, the mechanism of action of anti-CD20 therapy in autoimmune skin diseases is multi-level and involves not only the elimination of B cells but also broad modulation of the immune response. Processes leading to the reduction of autoantibodies, inhibition of T cell activation, reduction of inflammation in the skin, and reconstruction of a more tolerogenic B cell repertoire are crucial [5,6]. This comprehensive action makes anti-CD20 therapy one of the most effective and rational methods of treating autoimmune skin diseases, at the same time indicating directions for further development of targeted therapies that will be able to eliminate pathological immunological mechanisms even more selectively [26,49].

4.2 Anti-BAFF Therapies

The BLyS (B – lymphocyte stimulator) protein belongs to the TNF superfamily and stimulates the maturation and differentiation of autoreactive B lymphocytes and the production of autoantibodies. Overexpression of this protein is observed in SLE and other connective tissue diseases, especially during disease exacerbations [37] (belimumab – LymphoStat-B) and has been approved for the treatment of active, seropositive forms of the disease. The efficacy of belimumab was assessed in randomized, double-blind, placebo-controlled clinical trials involving over 1,600 patients with SLE. Patients with active and seropositive SLE (SELENA-SLEDAI >6 points; antinuclear antibody titer >1:80 and/or positive anti-dsDNA) were eligible for the studies. The two largest studies, BLISS-52 and BLISS-72, were conducted for 52 and 72 weeks, respectively. Patients were randomized to three groups: placebo, belimumab at a dose of 1 mg/kg, and 10 mg/kg. Throughout the study, patients received stable doses of glucocorticoids (GCs) and/or other immunosuppressive medications: chloroquine, methotrexate, mycophenolate mofetil (MMF), and azathioprine. The primary endpoint was improvement in the composite endpoint (SRI – Systemic Lupus Erythematosus Responder Index) at week 52 of treatment. Improvement in the SRI included a 4-point reduction in disease activity on the SELENA-SLEDAI scale, no worsening of the PGA (Physical Global Assessment), and no SLE exacerbation on the BILAG scale (no symptoms of SLE exacerbation meeting BILAG A criteria and/or no more than 1 BILAG B exacerbation). At week 52 of the study, 50.6% of patients receiving belimumab at a dose of 10 mg/kg/body weight and 38.8% of patients receiving placebo achieved the composite endpoint ($p < 0.0001$). The effect of belimumab at a dose of 10 mg/kg/body weight and 1 mg/kg body weight occurred after 16 and 28 weeks of treatment, respectively. Belimumab also reduced titers of anti-dsDNA and anticardiolipin antibodies and normalized complement C3 and C4 levels. The greatest benefits from belimumab treatment were observed in patients with high disease activity (SELENA-SLEDAI >10 points), low complement levels, and elevated anti-dsDNA titers, who were taking corticosteroids. In the combined analysis of both studies (BLISS-52 and BLISS-72), the percentage of patients whose corticosteroid dose was reduced by at least 25% to an equivalent dose of <7.5 mg prednisone was 17.9% in the belimumab group and 12.3% in the placebo group ($p = 0.04$). The effect of belimumab in patients with neuropsychiatric lupus erythematosus or severe lupus nephritis (i.e., SLE) was not studied – exclusion criteria were met. However, a post hoc analysis showed a reduction in the overall number of mild/moderate exacerbations compared to placebo ($p < 0.03$). The frequency of adverse events was comparable between the placebo and belimumab groups. Respiratory infections and infusion reactions were the most common. The effects of combination therapy with belimumab and cyclophosphamide or belimumab and another B-cell-targeted therapy have not been studied [37-40].

4.3 Bruton's Kinase (BTK) Inhibitors

Generally speaking, BTK inhibitors such as ibrutinib and rilzabrutinib are among the most promising therapeutic approaches in dermatology. Their rapid onset, IgE-independent mechanism, and favorable safety profile position them as strong candidates for expanding the therapeutic arsenal in several inflammatory dermatoses. As ongoing clinical trials mature, BTKs will likely gain an important—and perhaps preferred—role within therapeutic algorithms for certain phenotypes, offering effective and well-tolerated alternatives for patients with unmet needs [41].

In chronic spontaneous urticaria (CSU), the BTK target is particularly relevant due to its central role in mast cell activation via the FcεRI receptor. In Phase II and Phase III clinical trials, the drug demonstrated efficacy even in patients who had previously failed to respond to omalizumab, a clinically challenging subgroup often associated with less IgE-dependent mechanisms. The observation that remibrutinib maintained efficacy regardless of FcεRI expression or a prior anti-IgE response reinforces its potential utility in CSU phenotypes with type IIb autoimmunity [42].

4.4 Plasma Cell-Targeted Therapies

Plasma cells play a key role in the pathogenesis of autoimmune skin diseases, as they are responsible for the production of autoantibodies directed against skin and mucous membrane structures. In diseases such as pemphigus vulgaris, bullous pemphigoid, and systemic lupus erythematosus (SLE), autoantibodies are a major factor leading to tissue damage [5]. Therefore, plasma cells have become an important target for modern immune therapies. Of particular importance are long-lived plasma cells, which can survive for months or years in the bone marrow and chronically inflamed tissues [43]. These cells do not express the CD20 antigen and

therefore remain insensitive to rituximab and other anti-CD20 drugs [10]. This phenomenon partially explains the persistence of autoantibodies and the possibility of disease relapse despite effective B cell depletion.

In autoimmune skin diseases, plasma cells produce pathogenic immunoglobulins directed against:

- desmoglein 1 and 3 in pemphigus,
- BP180 and BP230 in pemphigoid,
- nuclear and cytoplasmic antigens in lupus erythematosus [5].

These autoantibodies activate complement, induce inflammatory infiltration, and lead to direct skin damage.

Proteasome Inhibitors

One of the best-known methods for eliminating plasma cells is the use of proteasome inhibitors, such as bortezomib. The mechanism of action of these drugs is based on blocking the 26S proteasome, which is responsible for the degradation of abnormal proteins within the cell [45]. Plasma cells, due to their very intense production of immunoglobulins, are particularly sensitive to disruptions in protein homeostasis.

Inhibition of the proteasome leads to:

- accumulation of abnormal proteins,
- endoplasmic reticulum stress,
- activation of apoptotic pathways,
- plasma cell death [45].

Clinical studies and case reports have demonstrated the efficacy of bortezomib in severe, resistant forms of:

- pemphigus vulgaris,
- lupus erythematosus,
- dermatomyositis [46].

This therapy can lead to a rapid decrease in autoantibody levels and clinical improvement even in patients resistant to rituximab.

However, the use of proteasome inhibitors is limited by side effects, such as:

- peripheral neuropathy,
- myelosuppression,
- increased risk of infection,
- hematological toxicity [47].

Anti-CD38 Therapies

A new approach to treatment is monoclonal antibodies directed against CD38, a marker of plasma cells. The best-known drug in this group is daratumumab, initially used in the treatment of multiple myeloma [48]. CD38 is highly expressed on:

- plasma cells,
- plasmablasts,
- some activated B lymphocytes.

Binding with CD38 leads to:

- antibody-dependent cytotoxicity (ADCC),
- complement activation,
- phagocytosis,
- induction of plasma cell apoptosis [48].

In recent years, reports have appeared on the efficacy of daratumumab in severe autoimmune skin diseases, particularly:

- refractory pemphigus,
- lupus erythematosus,
- autoimmune bullous diseases [49].

This therapy may be particularly beneficial in patients with persistent autoantibody production despite prior B cell depletion.

4.5 Cell-Based Therapies (CAR-T)

Recent studies of CAR T-cell therapies in autoimmune diseases have shown promising transitions from traditional, current drug regimens to potential single-dose therapies by targeting CD19 on B cells. By eliminating autoreactive B-cell clones along with all other B cells, the patient's immune system can reset itself, potentially restoring self-tolerance without interference from pathogenic clones that initiate disease. Clinical trials are currently actively investigating the efficacy of B-cell CAR T cells targeting CD19 and B-cell maturation antigen (BCMA) in a spectrum of autoimmune diseases, including systemic lupus erythematosus, myositis, pemphigus, multiple sclerosis, myasthenia gravis, and systemic sclerosis, with preliminary results indicating significant therapeutic benefit.[50]

Systemic Lupus Erythematosus (SLE)

Pioneering studies and subsequent case series provide compelling evidence of the potential of CD19-targeted CAR T cell therapy to induce durable remission in patients with refractory SLE, reshaping our understanding and treatment approach to autoimmune disease. Preliminary results from a single case study reported on a young adult woman with severe, refractory SLE who received fludarabine lymphatic system followed by low-dose autologous CD19 CAR T cell therapy [51]. Despite a refractory clinical course and multiple lines of therapy—including high-dose glucocorticoids, cyclophosphamide, mycophenolate mofetil, tacrolimus, belimumab, and rituximab—she experienced significant clinical and serologic improvement after CAR T cell therapy. Postinfusion, rapid CAR T cell expansion was observed, accompanied by complete but only transient B cell depletion. Clinically, this translated into resolution of proteinuria, normalization of serum complements levels, and a reduction in SLEDAI disease activity scores to zero [50].

Promising results from recent studies suggest that CD19 CAR T-cell therapy can provide sustained remission in SLE. With no reported serious adverse events and sustained serological remission, this therapy indicates a significant change in the trajectory of SLE disease. As such, CD19 CAR T-cell therapy is poised to transition from an experimental approach to a viable treatment for SLE, potentially revolutionizing the treatment of autoimmune diseases. However, additional comprehensive clinical trials and ongoing surveillance data are necessary to confirm its long-term safety and efficacy [50]

Systemic Sclerosis

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs, vasculopathy, and dysregulated immune responses [52]. This chronic condition can lead to devastating outcomes and poses significant treatment challenges when the disease progresses despite standard therapies [53]. Recently, a larger case series included four patients with SSc treated from February 2021 to May 2023, demonstrating the broader use of CD19 CAR T-cell therapy [54]. These patients, with persistent disease activity despite multiple immunosuppressive therapies, experienced rapid CAR T-cell expansion and complete B-cell depletion. All patients showed a decrease in EUSTAR activity without serious adverse events. These cases illustrate that CD19 CAR T-cells can be an effective approach to improving clinical outcomes in severe refractory SSc, particularly in those with cardiac and pulmonary involvement [50].

Chimeric T-cell Autoantibody Receptor (CAAR)

Several autoimmune diseases are directly caused by autoantibodies binding to self-antigens. These diseases are distinctive because their autoantibodies directly cause disease, unlike lupus, where, for example, double-stranded DNA antibodies are simply associated with disease and do not cause symptoms after passive transfer. This understanding led to the development of chimeric autoantibody receptor T-cell therapy (CAAR), which modifies the CAR-T approach to specifically recognize and kill pathogenic autoreactive B cells while sparing normal B cells essential for humoral immunity [55]. Currently, existing CAARs utilize the transmembrane and intracellular domains of clinically validated CARs but replace the scFv domain with the extracellular domains of the autoantigen to target autoantibody-expressing B cells [55]. The first described CAAR utilizes a portion of desmoglein 3 (Dsg3) as the extracellular domain to treat pemphigus vulgaris (PV), a bullous autoimmune disease caused by autoantibodies against the keratinocyte adhesion protein Dsg3. In an immune-active mouse model of PV, Dsg3 CAAR T cells selectively eliminated anti-Dsg3 B cells, reducing serum anti-Dsg3 autoantibody titers and improving blister formation [56]. Dsg3 CAAR T cells showed comparable efficacy to anti-CD19 CAR T cells in eliminating anti-Dsg3 B cells, even in the presence of soluble anti-Dsg3 antibodies [55].

Limitations of Therapy

One limitation of therapy is its possible relapse due to B cell repopulation or lack of plasma cell elimination. This means that autoantibodies may persist despite treatment, and the disease may recur after B cell repopulation [57]. Adverse effects and the risk of immunosuppression include an increased risk of infection (including severe infections). A higher rate of serious adverse events has been reported in bullous diseases than in other autoimmune diseases, as well as cases of sepsis and pneumonia in clinical trials, which is particularly significant in older adults and patients with comorbidities [58].

Another limitation is the heterogeneity of patient responses; efficacy depends on the disease phenotype, timing of treatment initiation, and individual immunological characteristics; a personalized approach is necessary [59].

Furthermore, the high costs of biological therapies or limited access to biological treatment must be considered. An additional limitation is the insufficient number of medical personnel working comprehensively in areas related to biological treatment.

10. Conclusions

Conclusions and Implications – The Importance of Plasma Cell-Targeted Therapies in Autoimmune Skin Diseases

Analysis of the role of B lymphocytes and plasma cells in the pathogenesis of autoimmune skin diseases leads to the clear conclusion that they are not only a supporting element of the immune response, but also a central source of maintaining the disease process. Of particular importance is the fact that in diseases such as pemphigus vulgaris, bullous pemphigoid, and lupus erythematosus, it is the long-lived plasma cells that are responsible for the continuous production of autoantibodies, which directly initiate and sustain tissue damage [10].

1. The Key Role of Plasma Cells as the "Source of Disease"

The most important conclusion is that:

- B lymphocytes are responsible for initiating the autoimmune response,
- while plasma cells are its persistent "end effector."

This means that even effective B cell elimination (e.g., with anti-CD20 therapy) does not always lead to complete disease resolution because:

- there are already established plasma cells,
- especially long-lived plasma cells in the bone marrow,
- that are independent of CD20 and resistant to many classic immunosuppressive therapies [10,56].

Clinical conclusion: autoimmune skin diseases have a "plasma cell" component that can sustain disease activity despite B cell elimination.

2. Limitations of anti-CD20 therapy as a rationale for plasma cell therapy

The use of rituximab and other anti-CD20 therapies represents a therapeutic breakthrough, but their effectiveness is limited by the fact that:

- they do not eliminate plasma cells,
- they do not fully remove autoantibodies already present in the body,
- they do not directly affect long-term humoral memory [10].

The consequences include:

- the possibility of disease relapse,
- persistence of autoantibodies despite B cell depletion,
- the need for repeated therapy or the use of combination therapy.

This leads to a fundamental conclusion:

Effective treatment of autoimmune skin diseases requires not only B cell blockade but also direct or indirect action on plasma cells.

3. Plasma cell-targeted therapies as the next stage in the evolution of immunotherapy

The development of therapies such as:

- proteasome inhibitors (e.g., bortezomib),
- anti-CD38 antibodies (e.g., daratumumab),
- anti-BCMA therapies,
- modulation of the BAFF/APRIL axis,
- represents a shift in the therapeutic paradigm from "B lymphocyte → antibody" to "plasma cell →

autoantibody" [45,48,60].

Conclusion:

These therapies enable a more "terminal" interruption of disease pathogenesis because they act closer to the final effector of immunological pathology.

4. Potential Advantages of Plasma Cell Therapies over Anti-CD20

Based on the available data, several potential advantages can be identified:

- more direct reduction of autoantibodies (reducing the source of their production),
- efficacy in cases resistant to rituximab,
- possibility of inducing deeper and longer remissions,
- effects even in the presence of established B-cell immunological memory [46,49].

At the same time, it should be emphasized that:

- the risk of immunosuppression is potentially higher,
- especially in the case of hypogammaglobulinemia and opportunistic infections,
- which limits the widespread use of these therapies in clinical practice [47].

5. The Concept of "Multilevel B-Cell Axis Blockade"

The most important immunopathological conclusion stems from the fact that:

autoimmune skin diseases are not a one-dimensional process, but involve several levels:

- B lymphocyte activation,
- differentiation into plasma cells,
- maintenance of long-lived plasma cells,
- autoantibody production,
- secondary activation of tissue inflammation.

Strategic Conclusion:

Effective future therapy should act at multiple levels, for example, through:

- B lymphocyte depletion (CD20),
- plasma cell elimination (CD38/BCMA/proteasome),
- and modulation of survival cytokines (BAFF/APRIL).

6. Clinical Significance and Future of Therapy

The current development of plasma cell therapies is leading to a shift in the treatment paradigm:

- from symptomatic and immunosuppressive treatment,
- toward source-directed therapy.

The most likely development directions include:

- combination therapies (CD20 + CD38 + BAFF),
- personalization of treatment depending on the dominant mechanism (B-cell vs. plasma-cell-driven disease),
- use of biomarkers (autoantibody levels, BAFF, plasma cell count).

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