CURRENT TOPIC

This article introduces a series of publications examining the pivotal challenge of inducing remission in autoimmune diseases through targeted depletion of autoreactive cells. The forthcoming publications will explore fundamental concepts in autoimmunity while identifying key therapeutic targets, alongside analyzing the most effective contemporary strategies for eliminating pathogenic cell populations.

Depletion-restitution therapy for autoimmune rheumatic diseases. Part 1. Fundamental prerequisites and efficacy of modern treatment technologies: anti-B-cell drugs and CAR-T therapy

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The key element in the pathogenesis of systemic autoimmune rheumatic diseases is the breakdown of immunological tolerance and the formation of a pool of autoreactive cells. This leads to uncontrolled activation of the effector arm of cellular (T-lymphocytes) and humoral (B-lymphocytes and plasma cells) immunity, proliferation of autoreactive clones, and the formation and persistence of immunological memory cells. In this process, T-cells, B-cells, and plasma cells of immunological memory, in interaction with a complex of pathogenic signals from the microenvironment, ensure the stability and adaptability of the developing inflammatory process.

In modern clinical practice, the prevailing approach to prescribing medications is the "therapeutic pyramid" strategy, which involves gradual escalation of treatment until remission is achieved. This approach does not address the mechanisms of immunological tolerance and, as a result, requires lifelong therapy and is associated with numerous adverse effects.

The term "depletion-restitution therapy" is proposed (from English "depletion" – exhaustion; and Latin "restitutio ad integrum" – restoration to the original state, complete recovery) to describe an alternative approach. This approach is characterized by methods based on massive, short-term cytotoxic impact, leading to profound reduction of pathogenic autoreactive cellular clones, followed by repopulation with "naive" cellular elements. Consequently, this restores tolerance mechanisms and enables the formation of ultra-long, drug-free remissions.

Currently, the principles of depletion-restitution therapy have already been integrated into oncology, hematology, and neurology. Among the most promising potential targets for such therapy in rheumatology are the effectors of the humoral immune system: B-cells, plasmablasts, and plasma cells. At the present stage, the most promising methods for implementing this approach are CAR-T cells and therapeutic bispecific monoclonal antibodies.

Key words: *depletion therapy; depletion-restitution therapy; B-cells; plasma cells; bispecific antibodies; monoclonal antibodies.*

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For reference: *Lila AM, Maslyanskiy AL, Dibrov DA, Torgashina AV, Zotkin EG, Samsonov MYu. Depletion-restitution therapy for autoimmune rheumatic diseases. Part 1. Fundamental prerequisites and efficacy of modern treatment technologies: anti-B-cell drugs and CAR-T therapy. Sovremennaya Revmatologiya=Modern Rheumatology Journal 2025;19(2):7–17.* ***DOI:*** *10.14412/1996-7012-2025-2-7-17*

Systemic autoimmune rheumatic diseases, the breakdown of immunological tolerance, and key effector cells

Systemic autoimmune rheumatic diseases (SARDs) constitute a complex interdisciplinary challenge in modern medicine due to their high prevalence, clinical and immunological heterogeneity, chronic disabling course, and limited treatment efficacy. The fundamental pathogenetic mechanism of these conditions involves immune system dysregulation leading to impaired central and peripheral immunological tolerance [1, 2]. This results in uncontrolled activation of cellular (T lymphocytes) and humoral (B lymphocytes and plasma cells) immune effector mechanisms, proliferation of autoreactive clones, and formation of persistent immunological memory cells. Importantly, memory T cells, B cells and plasma cells interacting with pathogenic microenvironmental signals maintain the stability and adaptability of ongoing inflammatory processes [3]. These alterations largely determine both the chronic

progressive nature of SARDs and the significant difficulties in achieving sustained remission in these diseases.

Current conventional disease-modifying therapies for SARDs, despite certain successes, generally demonstrate limited efficacy [4, 5]. They largely follow the "therapeutic pyramid" principle first proposed for rheumatoid arthritis (RA) treatment [6, 7]. Dose titration of conventional disease-modifying antirheumatic drugs (DMARDs), switching to alternative-mechanism agents when ineffective, and using various biologic DMARDs or drug combinations for refractory cases – all while monitoring disease activity and treatment tolerability (Treat-to-Target strategy) – in most cases provide control of immune-inflammatory activity. However, this approach fundamentally fails to restore immunological tolerance, necessitating indefinite (often lifelong) treatment. Certainly, such prolonged use of DMARDs, especially glucocorticoids, carries risks of chronic immunosuppression and metabolic disorders that depend not only on individual doses but also on cumulative drug exposure and treatment duration [8, 9].

A promising yet understudied therapeutic option for SARDs involves methods based on intensive short-term cytotoxic intervention leading to profound reduction of pathogenic autoreactive cell clones with subsequent repopulation from naïve cell populations and consequent restoration of tolerance mechanisms and induction of drug-free remission [10]. No established terminology currently exists for this approach in domestic or foreign literature, with various terms used: "depletion therapy", "pulsed immune reconstitution therapy", "immune reset" etc. We propose the term "depletion-restitution therapy" (DRT) [from depletion (English) - depletion, exhaustion; restitutio ad integrum (Latin) - complete restoration]. Various approaches have been developed to achieve this effect, including cyclic high-dose chemotherapy regimens, biologic DMARD therapies, modifications of autologous hematopoietic stem cell transplantation, and more recently – therapy with autologous modified T cells expressing chimeric antigen receptors (CAR) of varying specificity [11, 12].

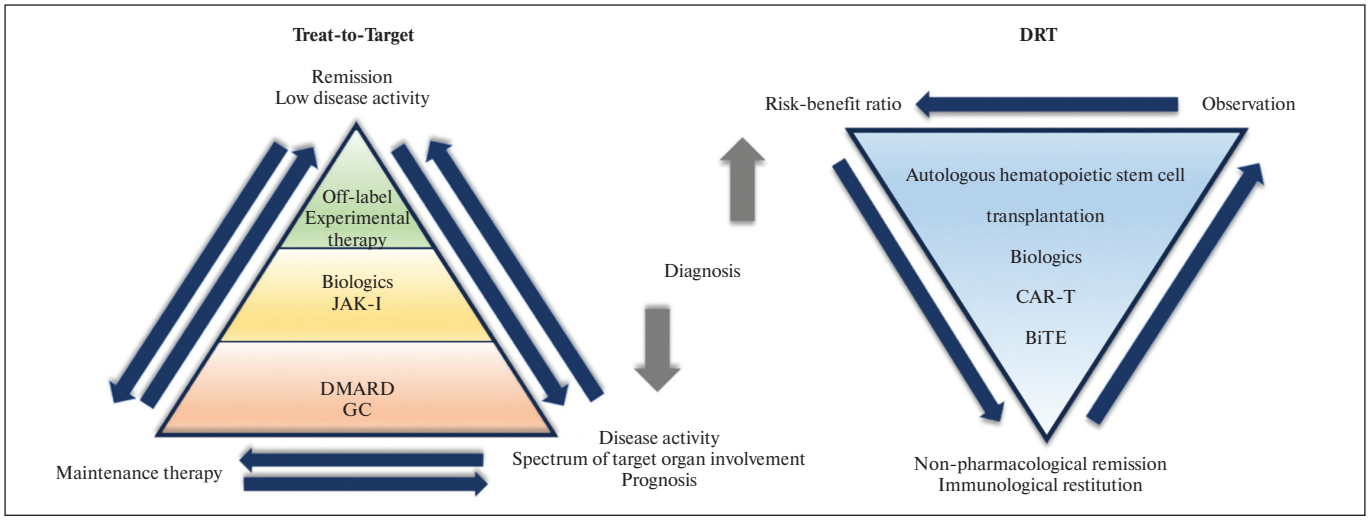
Substantial experience with DRT has been accumulated in the treatment of autoimmune demyelinating diseases of the central nervous system, particularly multiple sclerosis. Numerous randomized placebo-controlled trials have demonstrated that short-term cyclic administration of cladribine—a highly potent cytostatic agent causing sustained and profound B-lymphocyte depletion—or alemtuzumab—humanized monoclonal antibodies targeting CD52, a marker expressed by a broad range of immune cells (primarily mature T and B lymphocytes)—exerts a significant disease-modifying effect [13]. Although brief courses of these therapies carry risks of adverse events (AEs), particularly infections, they often enable prolonged drug-free remission lasting several years. Notably, M. Hecker et al. [14] conducted transcriptome analysis revealing substantial functional differences between circulating B cells before depletion therapy and after repopulation, supporting the concept of immune system "resetting."

Autologous hematopoietic stem cell transplantation (HSCT) in refractory SARDs — primarily multiple sclerosis and systemic sclerosis (SSc) — has also shown promising long-term outcomes, including sustained drug-free remission and stabilization or regression of target organ damage. However, the high cost, technical complexity, and significant risks (infections, secondary malignancies, and organ toxicity, largely due to high-dose conditioning chemotherapy) remain major barriers to widespread adoption [15, 16].

Effector Cells of the Humoral Immune System (B Cells, Plasma Cells) as Promising Targets for DRT in SARDs

B cells play a central role in the immunopathogenesis of SARDs. The survival, proliferation and expansion of autoreactive B-cell clones are associated with disturbances in central and peripheral tolerance mechanisms and underlie the initiation, chronicity and progression of self-sustaining inflammatory processes [1, 2, 17]. The pathogenic role of B cells is multifaceted and includes functions both dependent on and independent of autoantibody (autoAb) production.

The main autoantibody-dependent mechanisms in SARDs include: the production of pathogenic autoAbs (whose sources are descendants of B cells at various stages of maturity – plasmablasts and plasma cells, including long-lived ones), formation of immune complexes, antibody-dependent cell-mediated cytotoxicity, Fcγ receptor (FcγR)-mediated stimulation of immune cells, and complement system activation [17, 18]. Functions largely independent of autoAbs include the antigen-presenting function of B lymphocytes, their participation in neolymphogenesis mechanisms, synthesis of proinflammatory cytokines, effects on regulatory T cells (Tregs), and finally, T cell activation [18]. The wide range of biological



Comparison of Therapeutic Approaches for SARDs

effects mediated by B cells explains the influence of anti-B-cell therapy not only on the humoral but also on the cellular arm of immunity.

The role of B cells has been most extensively studied in the pathogenesis of rheumatoid arthritis (RA) and systemic connective tissue diseases. AutoAbs are detected in 70–80% of RA patients, with the main RA-specific autoAbs being those targeting the Fc fragment of IgG (IgM rheumatoid factor – RF) and cyclic citrullinated peptide (ACCP) [19, 20]. It has been shown that IgM RF and ACCP participate in the formation of immune complexes in synovial tissue with subsequent macrophage stimulation and proinflammatory cytokine production [21]. ACCP levels correlate with the number of cells bearing B-cell receptors specific for citrullinated proteins [22]. The main cell subpopulations producing anti-citrullinated protein autoAbs and/or expressing B-cell receptors of corresponding specificity are post-germinal center memory B cells, plasmablasts and plasma cells [23]. Subsequently, B cells migrate to synovial tissue where, under the influence of the microenvironment in ectopic lymphoid structures, they undergo stimulation and differentiation with subsequent autoAb production [24–26]. Since patients with established RA demonstrate ACCP not only of IgG but also of IgM class, it is likely that continuous renewal of B cells takes place in the synovial tissue, maintaining the pathological process [27]. The pathogenic role of ACCP in RA is supported by experimental data indicating their contribution to joint destruction mechanisms [28].

B lymphocytes play a decisive role in the pathogenesis of systemic lupus erythematosus (SLE). This disease is associated with production of a wide spectrum of autoAbs, mainly targeting nuclear components (antinuclear antibodies) and phospholipids. Pathogenic autoAb production in SLE patients is linked to pathological survival, activation and proliferation of autoreactive B cells, disturbances in B-cell receptor signaling pathways, Toll-like receptors, PI3K/AKT, and dysregulation of BAFF, CD40, interleukin (IL) 21 and IL22 [29]. Excessive autoAb secretion with subsequent immune complex formation causes chronic tissue inflammation leading to organ damage.

The direct pathogenic role of many SLE-associated autoAbs has been well characterized, particularly anti-dsDNA antibodies in lupus nephritis pathogenesis, anti-blood cell antibodies causing cytopenias and autoimmune hemolysis, and antiphospholipid antibodies as effectors of secondary antiphospholipid syndrome [30–32]. RNA- and DNA-containing immune complexes stimulate Toll-like receptors promoting type I interferon overproduction – key cytokines universally involved in systemic connective tissue disease pathogenesis, especially SLE [33].

The important role of B cells in systemic sclerosis (SSc) pathogenesis is undisputed [34]. Increased B-cell content has been found in skin and lung biopsies from SSc patients [35, 36]. As in RA, ectopic lymphoid follicle formation occurs in affected organs [37]. SSc patients with progressive lung involvement show an increased CD19+ cell count in bronchoalveolar lavage [38]. Overall, SSc patients exhibit approximately 20% higher CD19 expression compared to healthy individuals [39].

Antinuclear autoAbs are present in over 90% of SSc patients. A wide spectrum of SSc-specific autoAbs has been characterized, with the most important and common being those targeting topoisomerase I (anti-Scl70), centromere proteins (CENP A/B/C) and RNA polymerases I and III. The autoAb profiles correlate with clinical SSc variants (diffuse or limited) and target organ involvement, while levels of some of them (anti-Scl70) correlate with disease activity, though their precise clinical and pathogenic roles remain incompletely understood [40].

Perhaps, even more significant is the ability of B cells to regulate fibrogenesis. These cells are key producers of many proinflammatory and profibrotic cytokines, particularly IL-6 and transforming growth factor β. B cells influence fibroblast and macrophage polarization and activation, promoting profibrotic phenotypes [41–43]. The contribution of B cells to pathological fibrosis and the disease-modifying potential of anti-B-cell therapy have been convincingly demonstrated in animal models of SSc [43].

Modern Anti-B-Cell Therapy. Rituximab and the Reasons for Its Limited Efficacy

The central role of B cells in the immunopathogenesis of SARDs has generated considerable interest in B-cell depletion as a therapeutic strategy. It is reasonable to hypothesize that many conventional drugs and treatment modalities used in rheumatology practice may exert their therapeutic effects, at least in part, through modulation of humoral immunity. Current clinical guidelines for the management of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjцgren's syndrome (SS), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides recommend the use of protocols incorporating cyclophosphamide, mycophenolate mofetil, and high-dose glucocorticoids (GCs) for patients with severe disease activity or life-threatening organ involvement [44]. A critical mechanism underlying the therapeutic efficacy of these agents involves their potent suppressive effects on B-cell subpopulations [45]. Cyclophosphamide treatment has been shown to induce depletion of total lymphocytes, including naive, double-negative, and unswitched memory B cells, while mycophenolate mofetil therapy leads to reduced levels of plasmablasts and plasma cells in peripheral blood [45]. These findings highlight the significant impact of conventional immunosuppressive regimens on B-cell homeostasis, suggesting that their clinical benefits may be mediated, at least in part, through modulation of pathogenic B-cell populations. The recognition of these mechanisms provides a rationale for the continued use of these agents in severe autoimmune conditions while also informing about the development of more targeted B-cell-directed therapies. The differential effects of various immunosuppressants on distinct B-cell subsets may explain their variable efficacy across different autoimmune diseases and clinical scenarios. Further characterization of these immunological effects could help optimize treatment strategies for patients with refractory diseases.

A promising approach to enhance selective B-cell depletion involves repurposing drugs from oncohematological practice, particularly rituximab (RTX), a chimeric monoclonal antibody targeting the CD20 receptor on B-lymphocytes that was originally developed for B-cell lymphoma treatment. Subsequent successful application of this drug in SARDs, especially in refractory rheumatoid arthritis (RA), established it as a potential therapy capable of effectively depleting autoreactive B-cell populations. The remarkable clinical outcomes provided the rationale for randomized controlled trials (RCTs) that led to RTX approval for several indications, including RA, granulomatosis with polyangiitis, and microscopic polyangiitis [46, 47]. Substantial clinical experience has since been accumulated with RTX therapy across various SARDs, both for approved indications and off-label use, particularly in patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjцgren's syndrome (SS), and other conditions [48].

RTX therapy has proven particularly beneficial in seropositive RA, especially in cases with extra-articular manifestations [49, 50]. Meta-analyses have demonstrated that RTX shows comparable efficacy to other biologic disease-modifying antirheumatic drugs (biologics), including tocilizumab and abatacept [51]. Registry data indicate that approximately 50% of RA patients achieve low disease activity or remission following RTX treatment [52–55]. While RTX is currently widely used off-label for SLE patients refractory to standard therapy [56–59], the drug fails to produce adequate responses in at least 30% of cases [57, 58]. Randomized controlled trials have shown that RTX treatment for SLE patients, both with and without lupus nephritis, did not yield the expected therapeutic benefits [60, 61]. Small clinical studies have reported RTX efficacy in diffuse cutaneous systemic sclerosis (SSc), particularly for skin and lung involvement [62, 63]. However, the double-blind RECITAL trial found RTX no more effective than cyclophosphamide for this indication [64].

Thus, the efficacy of RTX in RA and ANCA-associated vasculitis appears well-established, while reports of its positive effects in other SARDs further support its use as a pathophysiologically grounded therapy for this disease group. However, the limitations of RTX effectiveness in treating many SARDs have become evident. In the vast majority of patients, RTX fails to induce long-term remission, particularly drug-free remission. Consequently, following a period of clinical improvement, repeated cycles of RTX are required due to disease flare. The absence of a true, sustained "immune reset" effect is indirectly evidenced by the lack of seroconversion. Specifically, most SARD patients maintain pathogenic autoantibodies (ACCP, antinuclear, anticardiolipin, etc.) following anti-B-cell therapy with RTX, indicating persistent autoreactive cell clones and their repopulation [65–67]. Finally, while RTX demonstrates clinical benefits in connective tissue diseases such as SLE, SSc, idiopathic inflammatory myopathies, and SS, its efficacy proves insufficient for antiphospholipid syndrome. These limitations underscore the need to develop novel, more effective treatment approaches, particularly various forms of depletion-restitution therapy (DRT).

The failure to achieve effective immune reset with RTX therapy likely stems from several key factors. First, dynamic variability in CD20 expression, influenced by genetic and epigenetic factors [68], plays a significant role. Reduced CD20 expression has been associated with poor response to CD20-targeted therapies. This phenomenon was initially demonstrated in B-cell lymphomas, where RTX treatment served as a negative selection factor promoting the emergence of resistant CD20-negative B-cell subpopulations [69]. Second, CD20-targeted agents cannot directly affect certain pathogenic B-cell subsets and their differentiation products that play crucial roles in SARD pathogenesis – particularly plasmablasts, plasma cells, and some memory B-cell clones, especially tissue-resident populations. This limitation stems from the natural absence of CD20 expression on these cell types. Third, while RTX induces profound depletion of circulating B-cells, it fails to completely eradicate B-cell reservoirs in bone marrow and lymph nodes [70–72]. Furthermore, SARDs are characterized by formation of tertiary lymphoid structures (new lymphoid follicles in target organs) that remain relatively inaccessible to biologic therapies, contributing to persistent inflammatory activity [73,74]. Additionally, the limited efficacy of RTX in systemic diseases, particularly SLE, may relate to its dependence on complement activation and membrane attack complex formation for B-cell depletion. This mechanism is potentially compromised in conditions frequently associated with hypocomplementemia during periods of high disease activity [75,76].

Evolution of Anti-B-Cell and Anti-Plasma Cell Therapies

Novel therapeutic approaches are being actively developed to improve the efficacy of B-cell-targeted treatments for SARDs. The next-generation anti-CD20 monoclonal antibody, obinutuzumab, has demonstrated clinical effectiveness in systemic lupus erythematosus (SLE) in clinical trials [77]. The key advantage of obinutuzumab over rituximab is its ability to achieve more profound B-cell depletion through enhanced antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) mechanisms [78]. This superior efficacy profile stems from structural modifications of the antibody's Fc fragment, which significantly increase its affinity for FcγRIII receptors on effector cells [79].

Another strategy for enhancing anti-B-cell therapy involves targeting alternative cell surface markers. Currently, the most promising targets include specific markers of B-lymphocytes and plasma cells (CD19, CD38) as well as B-cell maturation antigen (BCMA).

CD19 is a glycoprotein of the immunoglobulin superfamily and a critical component of the B-cell receptor signaling complex, as it lowers its activation threshold [80]. This marker is expressed across a broad range of B-lymphocytes – from pre-B cells to early stages of plasma cell differentiation (plasmablasts) [80]. However, it is important to note that CD19 is not expressed by long-lived plasma cells.

The broader expression profile on cells and the functional significance of CD19 compared to CD20 make it a promising target for anti-B-cell therapy in autoimmune diseases. Currently, monoclonal antibodies targeting CD19 have been developed and approved by the U.S. Food and Drug Administration (FDA) for the treatment of neuromyelitis optica spectrum disorder (inebilizumab) and B-cell lymphomas (tafasitamab).

Neuromyelitis optica is an inflammatory autoimmune demyelinating disorder primarily affecting the optic nerve and spinal cord, characterized by the presence of aquaporin-4 antibodies [81]. In the N-MOmentum trial, inebilizumab significantly prolonged the time to relapse in patients with neuromyelitis optica compared to placebo [82]. Furthermore, inebilizumab has demonstrated efficacy in patients who experienced disease relapse despite prior rituximab (RTX) therapy [83]. A randomized, placebo-controlled study involving 28 patients provided preliminary evidence supporting the drug's efficacy in treating systemic sclerosis (SSc), along with a favorable safety profile [84]. Patients treated with inebilizumab achieved depletion of B-lymphocytes and plasmablasts, accompanied by improvements in the modified Rodnan skin score (mRSS). Additionally, results from a double-blind, placebo-controlled trial demonstrated the effectiveness of inebilizumab in IgG4-related disease, with the potential to induce remission and discontinue glucocorticoid therapy [85].

Another marker successfully utilized as a target for depletion-restitution therapy (DRT) in patients with SARDs is the CD38 protein. This glycoprotein plays a role in lymphocyte activation, differentiation, and proliferation [86]. CD38 is most actively expressed in the bone marrow (BM) and lymph nodes, primarily by T-lymphocytes, B-cell precursors, germinal center B-cells, and—most prominently—plasma cells [87]. Studies have shown that in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), the expression of CD38 on blood cells is significantly

higher in patients compared to healthy individuals [88, 89]. In RA patients, elevated CD38 expression has been observed not only in peripheral blood but also in synovial tissue [90].

Daratumumab, a monoclonal antibody targeting CD38, currently approved for multiple myeloma treatment [91], has shown promising yet limited results in rheumatic diseases despite strong pathophysiological rationale. In a single-center study by T. Alexander et al. [92], 10 patients with refractory systemic lupus erythematosus (SLE) treated with daratumumab for 9 months demonstrated reduced anti-dsDNA antibody levels along with significant clinical improvement: SLEDAI-2K decreased from 12 to 4, CLASI-A skin activity index from 6 to 0, and Clinical Disease Activity Index from 11.5 to 0, without reported serious adverse events. Another case series documented effectiveness in 5 out of 6 patients with severe lupus nephritis, showing SLEDAI-2K reduction from 10.8 to 3.6 over 12 months while enabling glucocorticoid tapering to 5 mg/day [93]. Additional reports describe successful outcomes in two refractory SLE cases with lupus nephritis, hemolytic anemia and thrombocytopenia that previously required blood product transfusions [94]. Notably, these patients had previously failed multiple conventional therapies including standard immunosuppressants (azathioprine, cyclosporine A, mycophenolate mofetil, cyclophosphamide), biologics (belimumab), and off-label B-cell therapies (rituximab, ocrelizumab, bortezomib) [93, 94]. The therapeutic effects of daratumumab may extend beyond plasma cell depletion, potentially involving direct action on T-lymphocytes [91] through both cytotoxic effects against CD38+ cells and immunomodulatory properties mediated by calcium transport modulation in CD4+ cells with subsequent IL-2 synthesis regulation [95].

BCMA (B-cell maturation antigen) is a protein expressed on the membranes of mature B-lymphocytes, plasmablasts, and plasma cells, existing in both membrane-bound and soluble forms. It belongs to the tumor necrosis factor receptor superfamily. The physiological function of membrane-bound BCMA involves the reception of key growth factors that regulate survival and proliferation processes in B-lymphocytes, plasmablasts, and plasma cells – specifically B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL), which are essential for cellular survival [96].

BCMA expression is intrinsically linked to B-cell activation processes. Consequently, this antigen is predominantly localized on the membranes of B-lymphocytes at late differentiation stages, including memory B-cell subpopulations and long-lived plasma cells. For these cell types, the signaling pathway mediated by this receptor is crucial, determining their differentiation and survival.

Current evidence supports the involvement of BCMA in the pathogenesis of both SLE and RA. Studies have demonstrated that SLE patients exhibit significantly higher BCMA expression on plasma cells compared to healthy controls. Furthermore, serum levels of soluble BCMA show a direct correlation with disease activity [97].

Similarly, RA patients demonstrated significantly elevated serum levels of soluble BCMA, which correlated with the activity of the immune-inflammatory process. Studies have revealed that in these patients, BCMA is also expressed on fibroblast-like synoviocytes – cells that play a pivotal role in mediating bone and cartilage destruction [98, 99].

The BCMA-targeting antibody-drug conjugate, belantamab mafodotin, which couples a monoclonal antibody with the cytotoxic agent monomethyl auristatin-F, has demonstrated efficacy in patients with multiple myeloma refractory to multiple lines of therapy and has been approved for this indication. However, due to its significant toxicity profile, alternative anti-BCMA approaches such as bispecific monoclonal antibodies and CAR-T cell therapy appear more promising for the treatment of SARDs.

DRT: CAR-T Cell and Bispecific Monoclonal Antibody Approaches

CAR-T cell therapy represents a groundbreaking approach that enables unprecedentedly effective depletion of target cells in both peripheral blood and tissues. This method is highly versatile, as it allows for the generation of diverse cytotoxic cell populations (tailored to specific clinical needs) through the engineering of de novo antigen-recognizing receptors. The CAR-T cell manufacturing process is complex and multi-staged, involving production of a viral vector encoding the CAR construct with desired specificity, isolation of patient T-cells via leukapheresis, In vitro modification (transfection) using the engineered vector, enabling expression of chimeric antigen receptors (CARs), lymphodepletion (typically using cyclophosphamide-fludarabine conditioning) to create hematopoietic niche space for CAR-T cell engraftment and expansion, final infusion of the CAR-T cell suspension into the recipient [17]. The modified cells, expressing novel antigen-recognition receptors, effectively repopulate in vivo and exert potent cytotoxic effects, achieving profound depletion of programmed target cells. Originally developed for treatment-refractory B-cell lymphoproliferative disorders, this approach initially utilized CD19-specific CAR constructs. Early clinical trials demonstrated unprecedented efficacy, establishing CAR-T therapy as a mainstay in oncohematology. Subsequent technological advances have yielded CAR vectors targeting other antigens (CD20, CD22, CD33, BCMA, etc.), significantly expanding its therapeutic applications in oncological practice.

CAR-T cell therapy undoubtedly represents one of the most promising approaches for treating a wide range of oncological diseases, yet its implementation faces considerable challenges. The production of personalized CAR-T cell constructs requires an extended manufacturing period spanning several weeks. Significant logistical hurdles arise from the need to transport patient-derived lymphocytes—or the patients themselves—to specialized, well-equipped medical centers capable of performing the necessary transfection, cell culture expansion, and biomass production steps. Additional concerns include the inherent toxicity, particularly genotoxicity, of the lymphodepleting chemotherapeutic agents used in pretreatment protocols. Furthermore, the substantial costs associated with this advanced technology present a major barrier to its widespread clinical use.

A significant concern associated with CAR-T cell therapy remains the substantial risk of complications. The potent cytolytic activity and cytokine-producing capacity of CAR-T cells can lead to severe, potentially life-threatening adverse events. These include tumor lysis syndrome and cytokine release syndrome, which occurs in 50–90% of treated patients, as well as immune effector cell-associated neurotoxicity syndrome (ICANS) with an incidence of 20–60%. Long-term complications may involve cytopenic syndromes, hypogammaglobulinemia or even agammaglobulinemia, and infectious complications (observed in 28–48% of cases) [17]. Of particular concern is the potential for malignant transformation of transfected cell clones leading to T-cell lymphomas. To date, 26 cases of CAR-T therapy-induced T-cell neoplasms have been reported, prompting the FDA to mandate that manufacturers of

viral vectors used in cell line production include a black box warning in their prescribing information [100].

Recent years have seen emerging experimental and clinical evidence suggesting the potential for achieving sustained, drug-free remission – and possibly even cure – in at least a subset of patients with autoimmune diseases, including the most severe forms of rheumatic pathology. While still limited to isolated case reports and small case series, the available data on CAR-T cell therapy (primarily targeting CD19 or BCMA antigens) as salvage treatment for refractory, progressive, life-threatening SARDs – including SLE, idiopathic inflammatory myopathies, systemic sclerosis, and ANCA-associated vasculitis – have demonstrated remarkable outcomes. Published reports indicate near-universal efficacy in this critically ill patient population, with achievement of durable drug-free remission typically maintained for ≥1 year at the time of publication [12]. A comprehensive analysis of current evidence and future prospects for CAR-T cell therapy in SARDs has been presented in the review by E.L. Nasonov et al. [17].

Conclusion

Thus, the clinical efficacy of CAR-T cell therapy in SARDs has not only provided new evidence supporting the promise of depletion-restitution approaches, but has also further validated effector cells of humoral immunity (B-lymphocytes, plasmablasts, and plasma cells) as optimal therapeutic targets. Preliminary data suggest a more favorable safety profile when using this methodology for autoimmune and rheumatic diseases compared to oncological indications, which is largely attributed to the smaller cellular pool requiring elimination. A series of randomized controlled trials (RCTs) have now been initiated to more precisely evaluate the potential of this technology in rheumatology practice.

Future improvements in CAR-T cell therapy safety may emerge through advanced chimeric receptor modifications such as Chimeric Autoantibody Receptor (CAAR) cells and Chimeric Autoantigen-T Cell Receptor (CATCR) constructs, which enable targeted elimination of autoreactive immune populations while potentially reducing risks of cytokine release syndrome, ICANS, and immunosuppression. However, the exorbitant costs, technical challenges, and significant complication risks associated with these engineered cell therapies have driven increasing interest in developing simpler, more standardized pharmacological alternatives for DRT in SARDs.

Among the most promising approaches is the development and clinical application of bispecific antibody-based therapeutics [101]. This treatment strategy will be examined in greater detail in our forthcoming publication.

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Received/Reviewed/Accepted
19.02.2025/05.04.2025/07.04.2025

Conflict of Interest Statement

The investigation has been conducted within scientific topic 125020501434-1.

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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