CURRENT ISSUE

Depletion-restitution therapy of autoimmune rheumatic diseases. Part 2. Perspectives on bispecific antibodies

Maslyanskiy A.L.[1-3], Dibrov D.A.[1], Lila A.M.[1,4], Torgashina A.V.[1], Zotkin E.G.[1], Samsonov M.Yu.[5], Togizbayev G.A.[6]

[1]V.A. Nasonova Research Institute of Rheumatology, Moscow; [2]Almazov National Medical Research Centre, Ministry of Health of Russia, Saint Petersburg; [3]St Petersburg State University, Saint-Petersburg; [4]Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow; [5]R-Pharm JSC, Moscow; [6]Kazakh National Medical University named after S.D. Asfendiyarov, Almaty

[1]34A, Kashirskoye Shosse, Moscow 115522, Russia; [2]2, Akkuratova Street, Saint Petersburg 197341, Russia; [3]7–9, Universitetskaya Embankment, Saint Petersburg 199034, Russia; [4]2/1, Barrikadnaya Street, Build. 1, Moscow 125993, Russia; [5]111, Leninsky Prospect, Moscow 119421, Russia; [6]94, Tole Bi Street, Almaty 720040, Kazakhstan

One of the most promising approaches to depletion-restitution therapy is the development and use of drugs based on bispecific monoclonal antibodies (bsAbs). Therapeutic bsAbs are genetically engineered biological products (biologics) based on immunoglobulin molecules capable of simultaneously binding multiple antigens, making them a promising platform for novel drugs. A specific type of such agent, which incorporates at least two antigen-binding (Fab) fragments within a single immunoglobulin molecule – one targeting a specific cell-surface receptor and the other binding and activating to the CD3ε domain of CD3 molecule of the T-cell receptor complex – has been termed a bispecific T-cell engager (BiTE).

Currently, BiTE molecules that engage effector cells of the humoral immune system are the most clinically advanced subclass of bsAbs. Their ability to deplete target cells in peripheral blood and tissues has been clearly demonstrated in the treatment of resistant hematological malignancies such as B-cell precursor acute lymphoblastic leukemia, various lymphoproliferative disorders, and plasma cell dyscrasias. Recent years have seen attempts to repurpose bsAbs for the treatment of refractory, prognostically unfavorable forms of systemic autoimmune rheumatic diseases (SARDs), supported by theoretical rationale, experimental evidence, and parallels with successful CAR-T cell therapy.

Beyond BiTEs, the bsAb platform also enables development of biologics with extended pharmacokinetics, multi-cytokine targeting potential for synergistic suppression of inflammation, and checkpoint-directed modulation of targeted cell functional activity.

Advantages such as standardized manufacturing, off-the-shelf availability, predictable pharmacokinetics (with a known and limited half-life), flexible dosing regimens enabling slow escalation of the dose, the possibility of individualizing treatment duration and dosing frequency, the feasibility of repeated treatment cycles, the option to discontinue therapy in case of adverse events, and the significantly lower cost of short low-dose treatment cycles compared to CAR-T cell therapy – all these make bsAb-based strategies a highly attractive priority for next-generation depletion-restitution therapies for SARDs.

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

Contact: *Danil Alekseevich Dibrov;* ***dibrovd995@gmail.com***

For reference: *Maslyanskiy AL, Dibrov DA, Lila AM, Torgashina AV, Zotkin EG, Samsonov MYu, Togizbayev GA. Depletion-restitution therapy of autoimmune rheumatic diseases. Part 2. Perspectives on bispecific antibodies. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2025;19(3):7–18.* ***DOI:*** *10.14412/1996-7012-2025-3-7-18*

This article continues a series of publications exploring the potential for achieving remission in autoimmune diseases through profound depletion of autoreactive cells. It is worth recalling that depletion-restitution therapy refers to strategies based on short-term, intensive cytotoxic interventions leading to deep reduction of pathogenic autoreactive cellular clones, followed by repopulation predominantly from "naive" cell populations. This process promotes the restoration of immune tolerance mechanisms and the induction of drug-free remission [1]. One of the most promising approaches within the framework of depletion-restitution therapy is the development and use of therapeutic agents based on bispecific monoclonal antibodies (BsAbs).

Characteristics of Bispecific Antibodies. Bispecific T-Cell Engagers (BiTE)

Therapeutic bispecific antibodies (BsAbs) are genetically engineered biological agents (biologics) based on immunoglobulin molecules that are capable of selectively binding to two distinct antigens simultaneously. This property makes BsAbs a promising platform for the development of novel therapeutic agents [2]. It is hypothesized that bispecific antibodies represent a natural component of the humoral immune response. Due to the ability of IgG4 subclass immunoglobulins to undergo Fab-arm exchange, naturally occurring antibodies capable of binding two different antigens are present under physiological conditions in the human body [3, 4].

Although their precise biological role and regulatory mechanisms remain incompletely understood, it is believed that natural bispecific antibodies exert anti-inflammatory effects.

The first biologic based on a bispecific antibody molecule was catumaxomab, which was approved for clinical use by the U.S. Food and Drug Administration (FDA) in 2009. This agent incorporated two distinct Fab fragments: one specific for the CD3 component of the T-cell receptor, and the other targeting the epithelial cell adhesion molecule EpCAM a tumor-associated antigen that is overexpressed in several epithelial malignancies [5]. Catumaxomab was intended for the treatment of refractory malignant ascites in cancer patients. However, due to the structural characteristics of its Fc fragment, intravenous administration of catumaxomab led to intense off-target activation of Kupffer cells, resulting in hepatotoxic reactions that could be life-threatening [6, 7]. Consequently, the drug could only be administered intraperitoneally, and its production was discontinued in 2017 for economic reasons. Nevertheless, this development provided a proof-of-concept for the therapeutic applicability of BsAb-based agents, a concept that has since been successfully implemented in clinical practice.

Therapeutic agents based on a similar principle incorporating multiple (at least two) antigen-binding (Fab) fragments within a single immunoglobulin molecule have been termed bispecific T-cell engagers (BiTEs). In these constructs, one Fab domain is specific for a target antigen expressed on the surface of target cells (which may include B-cell or plasma cell antigens), while the other Fab binds and activates the CD3ε domain of the CD3 complex, a key component of the T-cell receptor.

The mechanism of action of BiTE molecules involves the physical crosslinking of a target cell expressing the relevant antigen with a T lymphocyte, mediated by the binding of CD3 on the T-cell surface. Importantly, this T-cell activation occurs independently of major histocompatibility complex (MHC) restriction and does not require native T-cell receptor (TCR) specificity effectively enabling in vivo T-cell redirection [8]. The close proximity enforced by the BiTE molecule facilitates the formation of an immune synapse between the T lymphocyte and the target cell, resulting in selective cytolysis of the latter via T cell-mediated cytotoxic mechanisms [9]. This process is characterized by exceptionally high efficiency (cytotoxic signal amplification), which can be achieved even at very low concentrations of the BiTE molecule due to its mechanism of action.

A classical representative of this new generation of BiTEs and the first to enter broad clinical use—is blinatumomab, approved for clinical application in 2014 for the treatment of precursor B-cell acute lymphoblastic leukemia. Blinatumomab is a molecule composed of small antibody fragments with a molecular weight of approximately 55 kDa, capable of simultaneously binding CD3ε and CD19 [10]. Notably, this molecule lacks an Fc fragment, which prevents unwanted macrophage activation and complement system engagement. However, the absence of an Fc region also means that blinatumomab is not protected from catabolism by the neonatal Fc receptor (FcRn), resulting in a short plasma half-life (1.25 ± 0.63 hours in vivo), and necessitating continuous intravenous infusion for therapeutic administration [10, 11]. Blinatumomab has demonstrated high efficacy in patients with relapsed or refractory hematologic malignancies, particularly in those who have not responded to prior anti–B-cell therapies [12–14].

The mechanisms of action of BiTEs and CAR-T cell therapy are fundamentally similar, which accounts for both their comparable efficacy and their overlapping spectrum of adverse events (AEs). The principal toxicities associated with bispecific T-cell engagers include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In the longer term, patients may also experience cytopenic syndromes, hypogammaglobulinemia or agammaglobulinemia, and infections. As standardized pharmaceutical agents, BiTEs offer several pharmacological advantages: predictable pharmacokinetics, enhanced therapeutic controllability, gradual dose titration, and the ability to interrupt treatment if necessary. These features stand in contrast to CAR-T cells, which represent a "living drug" with fixed kinetics and irreversible in vivo activity once infused. As a result, T-cell engagers based on BsAbs are associated with a more favorable safety profile. It is also important to emphasize that, unlike CAR-T cell therapy, BiTE administration does not require prior lymphodepleting chemotherapy and is not associated with the risk of malignant transformation of the transduced clone. Moreover, similar to CAR-T cells but in contrast to therapies based on monovalent monoclonal antibodies BiTEs are capable of mediating effective depletion of target cells not only in the circulatory system, but also in tissue compartments, which is particularly critical for the treatment of diseases with tissue-resident immune pathology [15].

According to registration clinical trials conducted in patients with precursor B-cell acute lymphoblastic leukemia, CRS occurred in up to 16% of those treated with blinatumomab, with grade 3–4 CRS observed in only 2–6% of cases. ICANS was reported in 61% of patients, though most cases were mild in severity. Severe AEs were considerably less frequent (reported in 7–17% of cases), while infections occurred in approximately 25% of patients at various stages of therapy [14]. It must be emphasized that these data reflect treatment outcomes in a highly challenging population patients with refractory acute leukemia who had already undergone multiple cycles of intensive polychemotherapy. Therefore, these results should not be directly extrapolated to patients with SARDs, who typically exhibit better hematopoietic reserve and, importantly, a smaller B-cell burden requiring depletion. Experience with CAR-T cell therapy in autoimmune diseases has shown that under these conditions, both the risk and severity of CRS and ICANS are significantly reduced.

The high efficacy of blinatumomab, as demonstrated in randomized controlled trials and subsequently confirmed in real-world clinical practice, particularly in a severely ill cohort of patients with precursor B-cell acute lymphoblastic leukemia refractory to prior therapies, has been shown to be comparable to that of CAR-T cell therapy. This success has sparked significant interest in the development of novel BsAb constructs. Since 2020, there has been an explosive increase in the number of BsAb-based agents, resulting in the development of more than ten new therapeutic products intended for use in oncology, rheumatology, and ophthalmology (Figure 1). Currently, over 100 BsAb molecules with similar structural frameworks are in various stages of clinical development, highlighting the promising potential of this therapeutic strategy [16].

The structural versatility of BsAbs makes them a unique tool for addressing a wide range of clinical challenges and provides a foundation for the development of therapeutic agents with diverse mechanisms of action. For instance, it is feasible to engineer BiTE molecules whose Fab fragments are directed against alternative B-cell antigens such as BAFF-R (B-cell activating factor receptor), CD20, BCMA (B-cell maturation antigen), or GPRC5D. These

constructs can efficiently redirect T-cell cytotoxicity toward specific subpopulations within the humoral immune system, including B cells, plasmablasts, and plasma cells. Retention of the Fc fragment within the structure of such molecules can potentially result in agents with improved pharmacokinetic properties compared to blinatumomab, which lacks this domain. These approaches have already been successfully implemented in the development of several therapeutic agents, including glofitamab and epcoritamab (anti-CD3/CD20), which have been approved for the treatment of lymphoproliferative disorders, as well as teclistamab and elranatamab (anti-CD3/BCMA), and talquetamab (anti-CD3/GPRC5D), all of which have demonstrated high efficacy in patients with multiple myeloma refractory to standard therapies [17] (Figure 2). Given their mechanisms of action, these and similar agents appear to have strong potential for integration into rheumatologic practice, offering a novel therapeutic option for conditions involving pathogenic B cells or plasma cells.

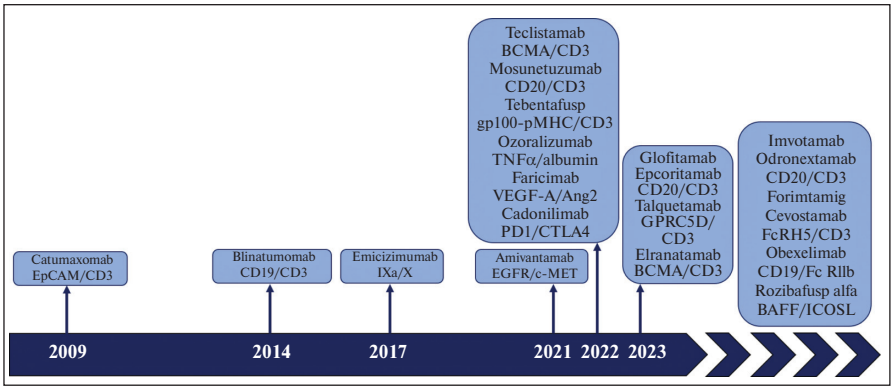

Fig. 1. *Chronological pipeline of bsAbs. TNFα – tumor necrosis factor alpha; VEGF – vascular endothelial growth factor*

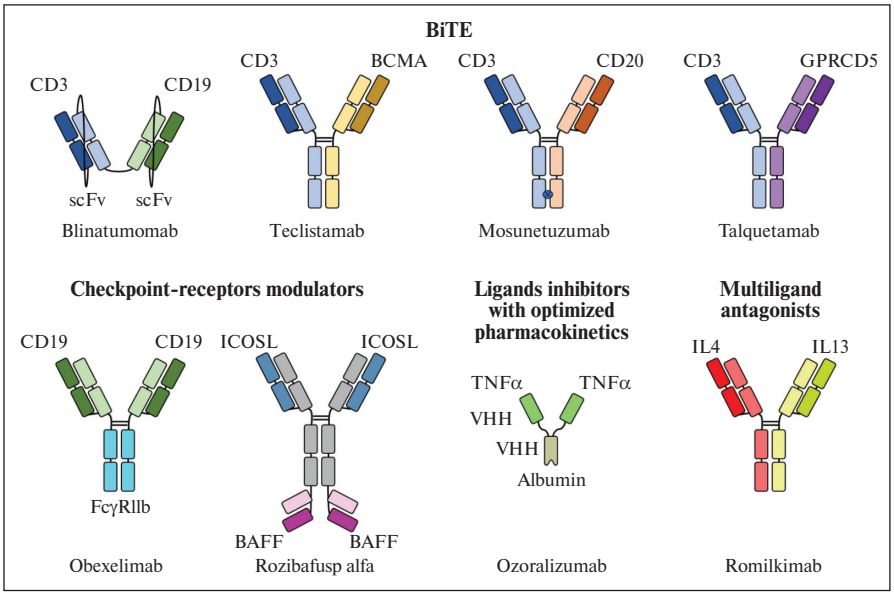

Fig. 2. *Variants of bispecific antibodies*

The strategic selection of target antigens enables the design of T-cell engagers that can selectively and effectively eliminate various immune cell populations, including activated clones of immunocompetent cells when activation markers are used as target antigens as well as T cells themselves [18]. One of the most compelling and currently experimental approaches involves the development of BiTEs that specifically recognize autoreactive lymphoid cells via their antigen receptor structures that detect epitopes of autoantigens. These molecules, termed bispecific autoantigen T-cell engagers (BiTEs), represent a conceptual advance in immunotherapy [19]. Implementation of this approach could potentially enable the development of depletion-based therapies capable of curing autoimmune diseases without inducing immunodeficiency.

In addition to BiTEs, BsAb technology also allows for the creation of other biologics with unique properties, such as optimized (extended) pharmacokinetics, the ability to simultaneously neutralize multiple cytokines to achieve synergistic effects, or the capacity to modulate the functional activity of specific immune cell populations by selectively interacting with checkpoint receptors that regulate cellular activation. The following sections present examples of successful implementation of these concepts.

The first genetically biologic based on BsAb technology to be approved for use in rheumatologic patients is ozoralizumab, which received official registration in Japan in 2022 and was authorized for the treatment of rheumatoid arthritis (RA) in that country. The ozoralizumab molecule is composed of three small fragments with a total molecular weight of approximately 38 kDa: two variable domains of heavy chains targeting tumor necrosis factor alpha (TNF-α), and one domain that binds to albumin [20]. This structural configuration characterized by low molecular weight and the absence of an Fc fragment confers several advantages over conventional TNF-α inhibitors, including improved tissue penetration and potentially reduced immunogenicity [21]. Binding to albumin ensures prolonged circulation of the drug in the bloodstream and facilitates its rapid distribution into inflamed tissues, particularly joints. The compact molecular structure and the absence of an Fc fragment significantly reduce the immunogenicity of ozoralizumab and minimize the risk of off-target activation of neutrophils and macrophages [22, 23]. A series of studies by Japanese researchers have demonstrated the high efficacy of ozoralizumab, both in combination with methotrexate and as monotherapy, as well as the flexibility in dosing regimens [24, 25].

Another genetically engineered biologic based on BsAb technology is rozibafusp alfa a bispecific molecule capable of simultaneously inhibiting ICOSL (Inducible Costimulator Ligand) and BAFF (B Cell Activating Factor) [26]. The therapeutic properties of this hybrid molecule are defined by its structural components: ICOSL plays a critical role in B–T cell interaction, mediating costimulation, germinal center formation, and the development

of ectopic lymphoid tissue [27]; BAFF, in turn, is essential for the survival of activated B cells [28]. Dual inhibition of ICOSL and BAFF by rozibafusp alfa demonstrated greater efficacy in experimental models of SARD) compared to the use of monospecific antibodies targeting either ICOSL or BAFF alone [26]. Results from a Phase I trial in rheumatoid arthritis, which enrolled 26 patients, showed satisfactory tolerability and preliminary efficacy of the drug compared to placebo [29]. Ongoing clinical trials are currently evaluating the efficacy and safety of rozibafusp alfa in the treatment of rheumatoid arthritis (NCT03156023) and systemic lupus erythematosus (NCT04058028).

Obexelimab is a monoclonal antibody that binds with high affinity to CD19 and features a modified Fc component, which significantly enhances its interaction with FcγRIIb by approximately 225-fold compared to IgG1 thereby enabling receptor modulation [30]. Due to this structure, obexelimab mimics antigen–antibody complexes, selectively targets B lymphocytes, and reduces their activity without inducing cytolytic effects [30]. Experimental studies in vitro and in vivo have confirmed the ability of obexelimab to suppress B-cell activity in healthy volunteers as well as in patients with systemic lupus erythematosus (SLE) [31]. A clinical trial evaluating obexelimab in SLE patients demonstrated good tolerability and safety [30].

A particularly promising application of obexelimab has been identified in the treatment of IgG4-related disease. In a pilot study, a clinical response was observed in 93% of patients, with 80% achieving the primary endpoint [32]. Ongoing research is currently evaluating the efficacy and safety of obexelimab in the treatment of IgG4-related disease (NCT05662241).

The combination of multiple Fab fragments targeting different antigens within a BsAb molecule may enhance therapeutic efficacy. For example, faricimab, used in ophthalmology, concurrently inhibits VEGF-A and angiopoietin-2, thereby more effectively suppressing neovascularization and inflammatory processes. Efforts are also underway to develop next-generation anti-cytokine agents based on BsAb platforms that can simultaneously block the physiological effects of two or more cytokines to achieve synergistic therapeutic outcomes. However, these approaches have generally yielded limited success to date.

Romilkimab is a bispecific IgG4 antibody whose Fab fragments neutralize interleukin (IL)-4 and IL-13, cytokines with profibrotic activity mediated through the recruitment, activation, and proliferation of fibroblasts, macrophages, and myofibroblasts [33, 34], as well as through upregulation of periostin expression [35]. However, initial hopes for the use of this agent in the treatment of idiopathic pulmonary fibrosis and systemic sclerosis (SSc) were not fulfilled [36, 37].

Repeated attempts to develop bispecific monoclonal antibodies capable of simultaneously inhibiting TNF-α and IL-17 have likewise been unsuccessful to date. Molecules such as COVA322, ABT-122, and JNJ61178104 were designed for this purpose. While data on the pharmacokinetics and immunogenicity of COVA322 have been published, no results regarding its safety or efficacy have been reported, and its development was eventually discontinued [38]. Although both ABT-122 and JNJ61178104 demonstrated acceptable safety profiles [39], ABT-122 failed to demonstrate superiority over monospecific TNF-α inhibitors in terms of efficacy [40], and no published results on JNJ61178104 are currently available. M.A. Kroenke et al. [41] proposed that the size and epitope binding sites of such bioconstructs may critically influence immunogenicity and pharmacokinetics, potentially promoting the formation of anti-drug antibodies and immune complexes, thereby reducing therapeutic efficacy.

Experience and examples for clinical use of BiTEs in SARDs

At present, the most promising and rapidly expanding class of BsAbs remains BiTEs targeting effector cells of the humoral immune response. Their capacity to achieve effective depletion of target cells in both peripheral blood and tissue compartments has been convincingly demonstrated in the treatment of therapy-resistant subtypes of various hematologic malignancies. In recent years, due to the urgent need for novel therapeutic strategies for prognostically unfavorable forms of SARDs, along with a well-established theoretical and experimental foundation, and encouraging results from the use of a mechanistically similar approach CAR-T cell therapy several attempts have been made to repurpose existing BiTE agents for the treatment of rheumatic diseases.

Notably, in 2024, a European research group published the first case series describing the successful use of blinatumomab in six patients with difficult-to-treat rheumatoid arthritis (D2T RA) [42]. In all cases, the rationale for initiating blinatumomab therapy was persistent, unacceptably high disease activity despite exhaustion of all available therapeutic options. All six patients had previously failed to respond to methotrexate, leflunomide, TNF-α inhibitors, and multiple Janus kinase (JAK) inhibitors. Additionally, five of the six patients had received IL-6 inhibitors, and three had undergone treatment with both abatacept and rituximab.

A distinctive feature of these clinical observations was the use of blinatumomab in single doses significantly lower than those employed in routine hematologic practice (9 vs. 28 μg/m^2/day), as well as the administration of shorter treatment cycles (5 vs. 28 days). Specifically, the patients received only two 5-day infusion cycles of blinatumomab spaced one week apart, compared to the minimum of five 28-day cycles commonly used in oncohematology. As a result of this treatment regimen, all patients experienced a rapid reduction in RA activity, achieving clinical remission by week 12 (with the DAS28-CRP score [Disease Activity Score 28 based on C-reactive protein] decreasing from an average of 4.72 to 2.28 points). In three patients, synovial biopsies were performed before and after therapy, demonstrating B-cell depletion in the synovial tissue. According to flow cytometry data, all patients achieved complete depletion of peripheral blood B lymphocytes, including activated memory B-cell subsets, followed by repopulation predominantly by naive B cells.

Over a 24-week follow-up period, a sustained decline was observed in the levels of rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) antibodies, anti-modified citrullinated vimentin (anti-MCV), and anti-carbamylated peptide antibodies. However, complete normalization of autoantibody levels was not achieved. The lack of seroconversion is likely attributable to the fact that the drug does not target long-lived plasma cells, which do not express the CD19 antigen. Blinatumomab therapy was well tolerated, with no serious adverse events necessitating treatment discontinuation. Three months after the final blinatumomab infusion, all patients resumed standard therapy.

German authors reported the successful use of blinatumomab in a 35-year-old female patient with diffuse systemic sclerosis (SSc) positive for anti-Scl70 antibodies [43]. The main indications for initiating this therapy were the rapidly progressive disease course, increasing severity of cutaneous induration, progression of Raynaud's phenomenon, and cardiac involvement (manifested by arrhythmias and increasing myocardial fibrosis as assessed by

cardiac magnetic resonance imaging), which were not adequately controlled with standard therapy. The latter included moderate doses of glucocorticoids (GCs) in combination with azathioprine, followed by a switch to mycophenolate mofetil. An important factor influencing the choice of treatment was the patient's intention to become pregnant. In this context, the short half-life of blinatumomab (hours) represented a clear advantage. The patient received two 5-day infusion cycles of blinatumomab at a dose of 9 μg/m^2/day, followed by one 5-day cycle and one 10-day cycle at 28 μg/m^2/day. Peripheral B-cell depletion was confirmed by flow cytometry. As a result of treatment, the patient demonstrated a rapid, significant, and sustained clinical improvement over a 4-month period, including resolution of skin induration, increased joint mobility, a decrease in the modified Rodnan skin score from 21 to 12, reduced frequency and severity of Raynaud's attacks, and stabilization of cardiac involvement, all while allowing for rapid de-escalation of concomitant therapy. The treatment was well tolerated, and as in previous reports no significant signs of CRS or ICANS were observed.

Alongside the use of T-cell–engaging BsAbs targeting CD19, the first clinical data on anti-BCMA therapy in patients with rheumatic diseases were published in 2024. Specifically, these reports involved teclistamab, an anti-CD3/BCMA bispecific T-cell engager, which had first been approved in 2022 for the treatment of patients with relapsed and refractory multiple myeloma [44]. By targeting BCMA (B-cell maturation antigen), a marker expressed on plasma cells, teclistamab demonstrated unprecedented therapeutic efficacy in multiple myeloma, achieving durable treatment responses in 63% of cases. Furthermore, minimal residual disease negativity indicative of profound tumor cell depletion was achieved in 27.6% of patients following teclistamab therapy. The pharmacokinetic properties of teclistamab supported subcutaneous administration, and to minimize the incidence and severity of adverse events, a step-up dosing regimen was employed.

As with blinatumomab, the most common AEs associated with teclistamab included CRS (reported in 61–72% of patients overall, with grade 3 severity in 0.6%), ICANS (in 3% of patients, all cases of mild to moderate severity), cytopenias, and infections (occurring in 76.4% of patients, with serious infections in 44.8%) [44]. Of particular interest, given the drug's mechanism of action, is the development of hypogammaglobulinemia, reported in 74.5% of cases. Consequently, approximately half of the patients required intravenous immunoglobulin (IVIG) replacement therapy.

The first clinical case of teclistamab use in rheumatology was described in a 23-year-old female patient with refractory SLE complicated by life-threatening multi-organ involvement [45]. The disease activity remained uncontrolled despite intensive combination therapy, including moderate to high doses of GCs, antimalarial agents, and sequential administration of immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, and voclosporin). Attempts to use biologic agents with various mechanisms of action (belimumab, anifrolumab) and intravenous immunoglobulin were also unsuccessful. Disease progression, particularly worsening lupus nephritis and severe anemia due to uncontrolled autoimmune hemolysis, necessitated salvage therapy. A five-week course of teclistamab was administered following a step-up dosing protocol. Mycophenolate mofetil was discontinued prior to initiating teclistamab. A rapid and marked clinical improvement was observed early in the course of anti-BCMA therapy. By week 2, arthritis regressed; by week 4, autoimmune hemolysis had completely resolved, along with resolution of cutaneous rash and oral ulcers. By week 5, anti-dsDNA antibody levels and complement activity normalized, and by week 6, proteinuria resolved. The SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index – 2K) decreased from 20 to 0 and remained at that level for the duration of follow-up. The induction of remission allowed for rapid tapering of GCs, which were completely discontinued by week 6 of therapy. Teclistamab administration was associated with several adverse events, including grade 2 CRS, which was effectively managed with tocilizumab (administered in week 2), and hypogammaglobulinemia leading to pneumonia and sinusitis, for which IVIG replacement therapy was initiated.

A group of German researchers [46] reported a series of clinical cases involving the use of teclistamab in four patients with RA, SSc, dermatomyositis, and Sjцgren's disease (SjD). A common feature among these patients was a high degree of resistance to more than five immunosuppressive agents, including rituximab, persistently high disease activity, and internal organ involvement. Teclistamab administration in all cases led to a rapid and complete reduction in disease activity, as well as stabilization or regression of organ involvement. In all patients, B-cell and plasmablast depletion in peripheral blood was confirmed and was accompanied by reductions in free light chain concentrations and in serum immunoglobulin levels across major classes. By week 12 of follow-up, signs of B-cell lineage repopulation were observed, characterized by an increase in naive, IgD-positive (non–class-switched) B lymphocytes, while memory B-cell depletion persisted. The sustained decrease in immunoinflammatory activity during the post-depletion period allowed for a reduction in pharmacotherapy, and all patients were able to discontinue immunosuppressive medications.

Thus, the results of clinical observations confirm the feasibility of implementing effective depletion–restitution therapy for SARDs using therapeutic BiTE antibodies targeting CD19 and BCMA antigens expressed on B lymphocytes and plasma cells. A distinctive feature of this therapeutic approach in patients with rheumatic diseases was the use of short treatment cycles, which enabled rapid reconstitution of the effector arm of humoral immunity. Additionally, the administration of lower single and cumulative doses contributed to better tolerability and reduced treatment costs. Preliminary evidence also supported the effective depletion of target cell populations not only in peripheral blood but also in affected tissues, a factor of critical importance for the induction of sustained drug-free remission.

At present, pharmaceutical companies have initiated the development of a new line of bispecific T-cell engager monoclonal antibodies intended for the treatment of autoimmune rheumatic diseases. Early-phase clinical trials have already been launched to evaluate the efficacy and safety of the bispecific antibody RO7507062 (anti-CD3/CD19), developed for the treatment of systemic lupus erythematosus (SLE) [47]. Studies have also begun on the novel anti-CD3/CD20 BiTE, imvotamab, in patients with rheumatoid arthritis (RA) (NCT06087406) and SLE (NCT06041568). Another possible scenario is the repurposing of some bispecific T-cell engagers already approved for use in oncohematological conditions for instance, a study of the CD3/CD20 BiTE mosunetuzumab in patients with SLE has been launched (NCT05155345).

Given the wide range of agents within this class both those recently approved for clinical use and those currently in late-stage clinical development the prospects for rapidly developing therapies based on these agents to implement depletion–restitution strategies for severe forms of rheumatic diseases appear both

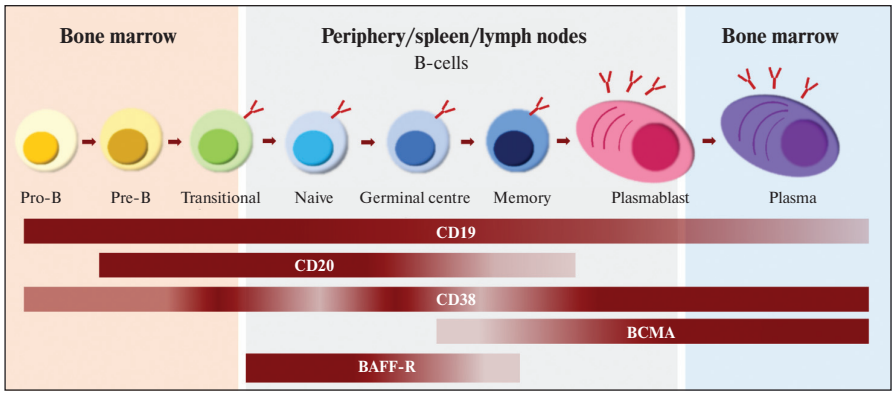

Fig. 3. *Therapeutic structures – B-cell targets (adapted from [49])*

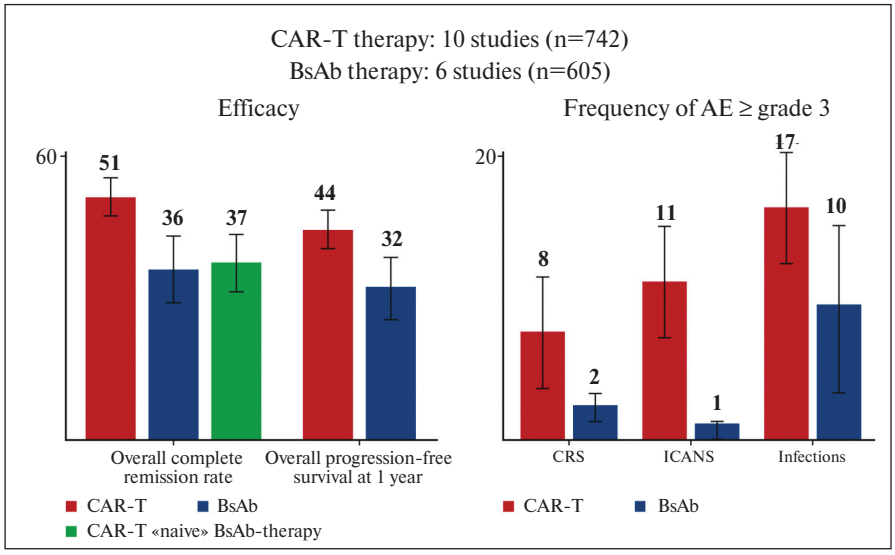

Fig. 4. *Comparison of efficacy and adverse reaction frequency in anti-CD19 CAR-T therapy vs. BiTE (adapted from [50]), %*

realistic and promising. Among the most prospective candidates are molecules targeting B-cell markers (such as epcoritamab, glofitamab, and odronextamab) as well as those directed against plasma cell markers, including anti-BCMA (elranatamab), anti-GPRC5D (talquetamab and forimtamig), and anti-FcRH5 (cevostamab) [48].

A critical consideration in selecting targeted biologic therapies for SARDs is the variability of therapeutic target expression at different stages of B-cell maturation. These data are summarized in Figure 3.

Comparative characteristics of CAR-T cell therapy and BiTEs

Proven manufacturing technologies, the potential to design agents targeting an almost unlimited range of antigens, successful experience in hematological practice, as well as the promising results demonstrated in pilot studies for the treatment of SARDs, position T-cell engagers and CAR-T therapies targeting effectors of the humoral immune response as the most promising candidates for the development of novel depletion-restitution therapeutic strategies in SARDs. However, the question of comparative advantages and limitations of both technologies remains open. This is primarily due to the relatively recent integration of these approaches into clinical practice and their initial use in the most severe, often treatment-refractory patient populations as "rescue therapy." These factors, together with the technical complexity of manufacturing CAR-T cell products, have complicated the design and execution of direct comparative studies. As a result, current comparisons of efficacy and safety between these approaches rely mainly on indirect data. Protocols evaluating anti-CD19 CAR-T cell therapies and anti-CD19 bispecific T-cell engagers in patients with B-cell lymphomas have been presented in several studies published in recent years (Figure 4).

Although the indirect nature of the comparison does not allow for definitive conclusions, available data suggest that CAR-T cell therapy may demonstrate somewhat higher efficacy compared to BiTEs. However, this is accompanied by a significantly greater toxicity profile associated with the CAR-T approach [51]. At the same time, these findings are preliminary and cannot be extrapolated to the use of BiTE constructs, including those with different antigen specificities, or to the application of such approaches in the treatment of SARDs. Nevertheless, in the context of their potential use in rheumatologic practice, the relatively lower toxicity of BiTEs could represent a critical advantage. We attempted to compare the key characteristics of CAR-T cell therapy and BiTE technologies that may determine their future applicability in rheumatology (see table).

Thus, CAR-T cell therapy represents a promising tool primarily in antitumor treatment; however, its extremely high cost and the risk of complications may potentially limit its widespread use in the therapy of autoimmune diseases, including rheumatic disorders. At the same time, the technology for generating therapeutic BiTEs offers broad opportunities for the development of classical biologic immunomodulatory drugs targeting various subpopulations of key immune-competent cells, primarily effectors of the humoral immune response, which can be successfully employed in the treatment of SARDs. The ease of standardizing BiTE-based drugs, the absence of the need to manufacture the drug de novo for each patient, the possibility of immediate administration (eliminating any time lag), predictable pharmacokinetics (a known and limited half-life), flexibility in dosing regimens allowing gradual dose escalation, the ability to individualize treatment duration and course frequency, the potential for easy and accessible repeated treatment cycles if necessary, the option to discontinue the drug in case of adverse reactions, and a substantially lower cost of short-cycle low-dose therapy compared to CAR-T cell therapy all represent defining advantages of this technology for developing new drugs for depletion-restitution therapy of SARDs.

Thus, CAR-T cell therapy represents a promising tool primarily in antitumor treatment; however, its extremely high cost and the risk of complications may potentially limit its widespread use in

Comparison of BiTE and CAR-T characteristics in clinical practice

Depletion-restitution therapy	BiTE	Autologic CAR-T cells
Ability to effectively eliminate blood and tissue pools of target cells	+++	++++
Manufacturing intricacies and characteristics of use	Standard monoclonal antibody manufacturing technologies. Drugs are immediately available in ready-to-use form	Individualized manufacturing for each patient. Treatment is delayed by 4–6 weeks due to the need to produce the drug. Logistical complexity
Standardization	Feasible	Complex; patient-specific product required
Mechanism of cytolytic activity	All patient T cells may potentially participate in the cytolytic elimination of target cells	The cytolytic activity is constrained by the number of transfected T cell clone
Pharmacokinetics	Standard, predictable, with the possibility of individualized treatment protocols and slow dose escalation	Unpredictable, uncontrollable ("living drug"). The number of CAR-T cell clones in the recipient's body is influenced by the efficiency of their proliferation *in vivo* and the duration of their persistence
Route of administration	Intravenous and subcutaneous. Possible outpatient administration, potentially self-administration. Short-term cyclical treatment	Intravenous only. Single treatment
Requirement for lymphodepletion in the therapy protocol	No	Yes
Safety	CRS and ICANs (usually low-grade). Toxicity can be limited by slow dose escalation	CRS and ICANs (possibly high-grade). Genotoxicity of lymphodepletion regimens. Risk of malignant transformation of the transduced clone
Pharmacological management methods for CRS and ICANS	GCs, IL6 and IL1 inhibitors	GCs, IL6 and IL1 inhibitors
Risk of irreversible immunosuppression	Low with short-term use	Higher, possibly associated with prolonged persistence of the CAR-T cell clone
Availability of approved drugs	Yes	Yes
Cost (based on data from approved indications) [52, 53]	Blinatumomab – 89 000 $ cycle, epcoritamab – 37 500 $ cycle, glofitamab – 41 176 $ cycle, teclistamab – 464 128 $ per year and 38 300 $ for one cycle (5 weeks)	350 000–500 000 $
Prospects for development of drugs selectively targeting autoreactive clones	Yes. BaiTE	Yes. CAAR, CATCR

Note. CAAR – chimeric autoantibody receptor; CATCR – chimeric autoantigen T-cell receptor.

the therapy of autoimmune diseases, including rheumatic disorders. At the same time, the technology for generating therapeutic BiTEs offers broad opportunities for the development of classical biologic immunomodulatory drugs targeting various subpopulations of key immune-competent cells, primarily effectors of the humoral immune response, which can be successfully employed in the treatment of SARDs. The ease of standardizing BiTE-based drugs, the absence of the need to manufacture the drug de novo for each patient, the possibility of immediate administration (eliminating any time lag), predictable pharmacokinetics (a known and limited half-life), flexibility in dosing regimens allowing gradual dose escalation, the ability to individualize treatment duration and course frequency, the potential for easy and accessible repeated treatment cycles if necessary, the option to discontinue the drug in case of adverse reactions, and a substantially lower cost of short-cycle low-dose therapy compared to CAR-T cell therapy all represent defining advantages of this technology for developing new drugs for depletion-restitution therapy of SARDs.

Both technologies possess significant potential for further development. Among the promising concepts for improving CAR-T cell therapy are alternative methods of modifying donor cells, including in vivo approaches, which could potentially shorten the lag period before therapy initiation and help overcome logistical challenges. Another strategy involves precise molecular "tuning" of CAR-T cell receptors to target B-cell effectors expressing specific autoantibodies and receptors, achieved, in particular, by incorporating autoantigenic epitopes directly into the CAR or T-cell receptor structure. This enables selective depletion of exclusively autoreactive cells (CAAR, CATCR) [54–56].

A similar principle was employed in the development of prototype molecules of new bispecific T-cell engagers specifically targeting autoreactive clones of B lymphocytes and plasma cells (BaiTE) [19]. The incorporation of autoantigenic epitopes into the Fc fragment structure of such constructs resulted in molecules

that activate T cells exclusively in the presence of autoreactive pathogenic cells, identified by their pre-known molecular receptor characteristics. This approach is expected to significantly reduce the likelihood of cytokine-mediated adverse events (CRS, ICANS) and the severity of immunosuppression. Initial experimental data have already demonstrated the selective depletion of humoral immune effectors autoreactive B cells specific to β2-glycoprotein 1 and phospholipase A2, the latter being a key factor in the pathogenesis of membranous nephropathy using T-cell engager molecules constructed based on this principle [19, 57]. This opens broad prospects for the treatment of antiphospholipid syndrome, membranous nephropathy, and, in the future, a wide range of other autoimmune diseases.

Conclusion

Although depletion-restitution therapy methods are still in early stages of development and require further refinement, it is evident that their implementation has the potential to fundamentally shift the treatment paradigm. This shift would move away from the use of insufficiently effective therapies that fail to alter the disease course significantly, towards approaches aimed at modifying the fundamental pathogenic mechanisms of SARDs. Therapeutic BsAb-based drugs appear to be the most promising tools for the rapid implementation of such an approach. Moreover, the principles underlying the BsAb structure can be successfully applied to improve already existing classes biologics, including anti-cytokine agents and costimulatory molecule inhibitors.

REFERENCES

1. Ramirez-Valle F, Maranville JC, Roy S, Plenge RM. Sequential immunotherapy: towards cures for autoimmunity. *Nat Rev Drug Discov*. 2024 Jul;23(7):501-524. doi: 10.1038/s41573-024-00959-8. Epub 2024 Jun 5.
2. Shah K, Leandro M, Cragg M, et al. Disrupting B and T-cell collaboration in autoimmune disease: T-cell engagers versus CAR T-cell therapy? *Clin Exp Immunol*. 2024 Jun 20;217(1):15-30. doi: 10.1093/cei/uxae031.
3. Van der Neut Kolfschoten M, Schuurman J, Losen M, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science*. 2007 Sep 14;317(5844):1554-7. doi: 10.1126/science.1144603.
4. Rispens T, Huijbers MG. The unique properties of IgG4 and its roles in health and disease. *Nat Rev Immunol*. 2023 Nov;23(11):763-778. doi: 10.1038/s41577-023-00871-z. Epub 2023 Apr 24.
5. Heiss MM, Murawa P, Koralewski P, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: Results of a prospective randomized phase II/III trial. *Int J Cancer*. 2010 Nov 1;127(9):2209-21. doi: 10.1002/ijc.25423.
6. Seimetz D, Lindhofer H, Bokemeyer C. Development and approval of the trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) as a targeted cancer immunotherapy. *Cancer Treat Rev*. 2010 Oct;36(6):458-67. doi: 10.1016/j.ctrv.2010.03.001. Epub 2010 Mar 27.
7. Borlak J, Langer F, Spanel R, et al. Immune-mediated liver injury of the cancer therapeutic antibody catumaxomab targeting EpCAM, CD3 and Fcgamma receptors. *Oncotarget* 2016;7(19):28059-74. doi: 10.18632/oncotarget.8574.
8. Labrijn AF, Janmaat ML, Reichert JM, Parren P. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov*. 2019 Aug;18(8):585-608. doi: 10.1038/s41573-019-0028-1.
9. Offner S, Hofmeister R, Romaniuk A, et al. Induction of regular cytolytic T cell synapses by bispecific single-chain antibody constructs on MHC class I-negative tumor cells. *Mol Immunol*. 2006 Feb;43(6):763-71. doi: 10.1016/j.molimm.2005.03.007. Epub 2005 Apr 26.
10. Loffler A, Kufer P, Lutterbuse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. *Blood*. 2000 Mar 15;95(6):2098-103.
11. Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood*. 2016 Mar 17;127(11):1410-6. doi: 10.1182/blood-2015-06-651380. Epub 2016 Jan 11.
12. Boissel N, Chiaretti S, Papayannidis C, et al. Real-world use of blinatumomab in adult patients with B-cell acute lymphoblastic leukemia in clinical practice: results from the NEUF study. *Blood Cancer J*. 2023 Jan 4;13(1):2. doi: 10.1038/s41408-022-00766-7.
13. Thompson PA, Jiang X, Banerjee P, et al. A phase two study of high dose blinatumomab in Richter's syndrome. *Leukemia*. 2022 Sep;36(9):2228-2232. doi: 10.1038/s41375-022-01649-3. Epub 2022 Aug 8.
14. Lantz J, Pham N, Jones C, et al. Blinatumomab in Practice. *Curr Hematol Malig Rep*. 2024 Feb;19(1):1-8. doi: 10.1007/s11899-023-00714-7. Epub 2023 Dec 7.
15. Blair HA. Odronextamab: First Approval. *Drugs*. 2024 Dec;84(12):1651-1658. doi: 10.1007/s40265-024-02112-6. Epub 2024 Nov 19.
16. Surowka M, Klein C. A pivotal decade for bispecific antibodies? *MAbs*. 2024 Jan-Dec;16(1):2321635. doi: 10.1080/19420862.2024.2321635. Epub 2024 Mar 11.
17. Strohl WR. Structure and function of therapeutic antibodies approved by the US FDA in 2023. *Antib Ther*. 2024 Mar 19;7(2):132-156. doi: 10.1093/abt/tbae007. eCollection 2024 Apr.
18. Caracciolo D, Mancuso A, Polera N, et al. The emerging scenario of immunotherapy for T-cell Acute Lymphoblastic Leukemia: advances, challenges and future perspectives. *Exp Hematol Oncol*. 2023 Jan 9;12(1):5. doi: 10.1186/s40164-022-00368-w.
19. Xia Y, Liu J, Pearlman A, et al. Bispecific Autoantigen-T Cell Engagers (BaiTE) to Selectively Target Autoreactive B Cells in Antiphospholipid Syndrome [abstract]. *Arthritis Rheumatol*. 2024;76(suppl 9):0837.
20. Tsumoto K, Takeuchi T. Next-Generation Anti-TNFalpha Agents: The Example of Ozoralizumab. *BioDrugs*. 2024 May;38(3):341-351. doi: 10.1007/s40259-024-00648-3. Epub 2024 Apr 8.
21. Ishiwatari-Ogata C, Kyuuma M, Ogata H, et al. Ozoralizumab, a Humanized Anti-TNF-alpha NANOBODY((R)) Compound, Exhibits Efficacy Not Only at the Onset of Arthritis in a Human TNF Transgenic Mouse but Also During Secondary Failure of Administration of an Anti-TNFalpha IgG. *Front Immunol*. 2022 Feb 22:13:853008. doi: 10.3389/fimmu.2022.853008. eCollection 2022.
22. Oyama S, Ebina K, Etani Y, et al. A novel anti-TNF-alpha drug ozoralizumab rapidly distributes to inflamed joint tissues in a mouse model of collagen induced arthritis. *Sci Rep*. 2022 Oct 27;12(1):18102. doi: 10.1038/s41598-022-23152-6.
23. Kyuuma M, Kaku A, Mishima-Tsumagari C, et al. Unique structure of ozoralizumab, a trivalent anti-TNFalpha NANOBODY((R)) compound, offers the potential advantage of mitigating the risk of immune complex-induced inflammation. *Front Immunol*. 2023 Apr 14:14:1149874. doi: 10.3389/fimmu.2023.1149874. eCollection 2023.
24. Tanaka Y, Miyazaki Y, Kawanishi M, et al. Long-term safety and efficacy of anti-TNF multivalent VHH antibodies ozoralizumab in patients with rheumatoid arthritis. *RMD Open*. 2024 Aug 22;10(3):e004480. doi: 10.1136/rmdopen-2024-004480.
25. Takeuchi T, Nakanishi M, Kawanishi M, et al. Effect of the extended dosing interval of anti-TNF-alpha NANOBODY(R) compound ozoralizumab in patients with low disease activity rheumatoid arthritis. *Mod Rheumatol*. 2024 Jul 6;34(4):678-685. doi: 10.1093/mr/road097.
26. Zhang M, Lee F, Knize A, et al. Develop-

ment of an ICOSL and BAFF bispecific inhibitor AMG 570 for systemic lupus erythematosus treatment. *Clin Exp Rheumatol.* 2019 Nov-Dec;37(6):906-914. Epub 2019 Feb 15.
27. Stefanski AL, Dorner T. Immune checkpoints and the multiple faces of B cells in systemic lupus erythematosus. *Curr Opin Rheumatol.* 2021 Nov 1;33(6):592-597. doi: 10.1097/BOR.0000000000000825.
28. Ferraccioli G, Gremese E. B cell activating factor (BAFF) and BAFF receptors: fakes and facts. *Clin Exp Immunol.* 2017 Dec;190(3): 291-292. doi: 10.1111/cei.13039. Epub 2017 Sep 28.
29. Abuqayyas L, Cheng LE, Teixeira Dos Santos M, et al. Safety and Biological Activity of Rozibafusp alfa, a Bispecific Inhibitor of Inducible Costimulator Ligand and B Cell Activating Factor, in Patients With Rheumatoid Arthritis: Results of a Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study. *ACR Open Rheumatol.* 2022 Oct;4(10):903-911. doi: 10.1002/acr2.11487. Epub 2022 Jul 27.
30. Chu SY, Vostiar I, Karki S, et al. Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcgammaRIIb with Fc-engineered antibodies. *Mol Immunol.* 2008 Sep;45(15): 3926-33. doi: 10.1016/j.molimm.2008.06.027. Epub 2008 Aug 8.
31. Horton HM, Chu SY, Ortiz EC, et al. Antibody-mediated coengagement of FcgammaRIIb and B cell receptor complex suppresses humoral immunity in systemic lupus erythematosus. *J Immunol.* 2011 Apr 1;186(7): 4223-33. doi: 10.4049/jimmunol.1003412. Epub 2011 Feb 28.
32. Perugino CA, Wallace ZS, Zack DJ, et al. Evaluation of the safety, efficacy, and mechanism of action of obexelimab for the treatment of patients with IgG4-related disease: an open-label, single-arm, single centre, phase 2 pilot trial. *Lancet Rheumatol.* 2023 Aug; 5(8):e442-e450. doi: 10.1016/S2665-9913(23)00157-1. Epub 2023 Jul 24.
33. Jakubzick C, Choi ES, Joshi BH, et al. Therapeutic attenuation of pulmonary fibrosis via targeting of IL-4- and IL-13-responsive cells. *J Immunol.* 2003 Sep 1;171(5):2684-93. doi: 10.4049/jimmunol.171.5.2684.
34. Rafii R, Juarez MM, Albertson TE, Chan AL. A review of current and novel therapies for idiopathic pulmonary fibrosis. *J Thorac Dis.* 2013 Feb;5(1):48-73. doi: 10.3978/j.issn.2072-1439.2012.12.07.
35. Izuhara K, Conway SJ, Moore BB, et al. Roles of Periostin in Respiratory Disorders. *Am J Respir Crit Care Med.* 2016 May 1; 193(9):949-56. doi: 10.1164/rccm.201510-2032PP.
36. Raghu G, Richeldi L, Crestani B, et al. SAR156597 in idiopathic pulmonary fibrosis: a phase 2 placebo-controlled study (DRI11772). *Eur Respir J.* 2018 Dec 13;52(6): 1801130. doi: 10.1183/13993003.01130-2018. Print 2018 Dec.
37. Allanore Y, Wung P, Soubrane C, et al. A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis. *Ann Rheum Dis.* 2020 Dec;79(12):1600-1607. doi: 10.1136/annrheumdis-2020-218447. Epub 2020 Sep 22.
38. Silacci M, Lembke W, Woods R, et al. Discovery and characterization of COVA322, a clinical-stage bispecific TNF/IL-17A inhibitor for the treatment of inflammatory diseases. *MAbs*. 2016;8(1):141-9. doi: 10.1080/19420862.2015.1093266. Epub 2015 Sep 22.
39. Khatri A, Othman AA. Population Pharmacokinetics of the TNF-alpha and IL-17A Dual-Variable Domain Antibody ABT-122 in Healthy Volunteers and Subjects With Psoriatic or Rheumatoid Arthritis: Analysis of Phase 1 and 2 Clinical Trials. *J Clin Pharmacol.* 2018 Jun;58(6):803-813. doi: 10.1002/jcph.1068. Epub 2018 Jan 24.
40. Khatri A, Klunder B, Peloso PM, Othman AA. Exposure-response analyses demonstrate no evidence of interleukin 17A contribution to efficacy of ABT-122 in rheumatoid or psoriatic arthritis. *Rheumatology (Oxford).* 2019 Feb 1;58(2):352-360. doi: 10.1093/rheumatology/key312.
41. Kroenke MA, Milton MN, Kumar S, et al. Immunogenicity Risk Assessment for Multi-specific Therapeutics. *AAPS J.* 2021 Nov 5;23(6):115. doi: 10.1208/s12248-021-00642-5.
42. Bucci L, Hagen M, Rothe T, et al. Bispecific T cell engager therapy for refractory rheumatoid arthritis. *Nat Med.* 2024 Jun; 30(6):1593-1601. doi: 10.1038/s41591-024-02964-1. Epub 2024 Apr 26.
43. Subklewe M, Magno G, Gebhardt C, et al. Application of blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, in treating severe systemic sclerosis: A case study. *Eur J Cancer.* 2024 Jun:204:114071. doi: 10.1016/j.ejca.2024.114071. Epub 2024 Apr 22.
44. Guo Y, Quijano Carde NA, Kang L, et al. Teclistamab: Mechanism of action, clinical, and translational science. *Clin Transl Sci.* 2024 Jan;17(1):e13717. doi: 10.1111/cts.13717.
45. Alexander T, Kronke J, Cheng Q, et al. Teclistamab-Induced Remission in Refractory Systemic Lupus Erythematosus. *N Engl J Med.* 2024 Sep 5;391(9):864-866. doi: 10.1056/NEJMc2407150.
46. Hagen M, Bucci L, Boltz S, et al. BCMA-Targeted T-Cell-Engager Therapy for Autoimmune Disease. *N Engl J Med.* 2024 Sep 5;391(9):867-869. doi: 10.1056/NEJMc2408786.
47. Kollert F, Regenass F, Hallet R, et al. AB1034 Characterization of RO7507062, A CD19-targeting T-cell bispecific antibody (CD19TCB), and design of a phase 1 trial in systemic lupus erythematosus. *Ann Rheum Dis.* 2024;83(Suppl 1):1837-1838. doi: 10.1136/annrheumdis-2024-eular.1802.
48. Van de Donk N, O'Neill C, de Ruijter MEM, Verkleij CPM, Zweegman S. T-cell redirecting bispecific and trispecific antibodies in multiple myeloma beyond BCMA. *Curr Opin Oncol.* 2023 Nov 1;35(6):601-611. doi: 10.1097/CCO.0000000000000983. Epub 2023 Jul 24.
49. Robinson WH, Fiorentino D, Chung L, et al. Cutting-edge approaches to B-cell depletion in autoimmune diseases. *Front Immunol.* 2024 Oct 9:15:1454747. doi: 10.3389/fimmu.2024.1454747. eCollection 2024.
50. Gurumurthi A, Westin J, Subklewe M. The race is on: bispecifics vs CAR T cells in B-cell lymphoma. *Blood Adv.* 2023 Oct 10; 7(19):5713-5716. doi: 10.1182/bloodadvances.2022009066.
51. Kim J, Cho J, Lee MH, et al. CAR T cells vs bispecific antibody as third- or later-line large B-cell lymphoma therapy: a meta-analysis. *Blood.* 2024 Aug 8;144(6):629-638. doi: 10.1182/blood.2023023419.
52. Trabolsi A, Arumov A, Schatz JH. Bispecific antibodies and CAR-T cells: dueling immunotherapies for large B-cell lymphomas. *Blood Cancer J.* 2024 Feb 8;14(1):27. doi: 10.1038/s41408-024-00997-w.
53. Насонов ЕЛ, Румянцев АГ, Самсонов МЮ. Фармакотерапия аутоиммунных ревматических заболеваний – от моноклональных антител к CAR-T-клеткам: 20 лет спустя. Научно-практическая ревматология. 2024;62(3):262-279. [Nasonov EL, Rumyantsev AG, Samsonov MYu. Pharmacotherapy of autoimmune rheumatic diseases – from monoclonal antibodies to CAR-T cells: 20 years later. *Nauchno-prakticheskaya revmatologiya* 2024;62(3):262-279. (In Russ.)].
54. Schett G, Muller F, Taubmann J, et al. Advancements and challenges in CAR T cell therapy in autoimmune diseases. *Nat Rev Rheumatol.* 2024 Sep;20(9):531-544. doi: 10.1038/s41584-024-01139-z. Epub 2024 Aug 6.
55. Mog B, Shaw E, Hwang M, et al. Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapies to Selectively Target Autoreactive B Cells [abstract]. *Arthritis Rheumatol.* 2022;74(suppl 9):1677.
56. Del Bufalo F, Becilli M, Rosignoli C, et al. Allogeneic, donor-derived, second-generation, CD19-directed CAR-T cells for the treatment of pediatric relapsed/refractory BCP-ALL. *Blood.* 2023 Jul 13;142(2): 146-157. doi: 10.1182/blood.2023020023.
57. Perico L, Casiraghi F, Sonego F, et al. Bi-specific autoantigen-T cell engagers as targeted immunotherapy for autoreactive B cell depletion in autoimmune diseases. *Front Immunol.* 2024 Feb 26:15:1335998. doi: 10.3389/fimmu.2024.1335998. eCollection 2024.

Received/Reviewed/Accepted
20.04.2025/27.05.2025/30.05.2025

Conflict of Interest Statement

This work was conducted within the framework of the basic research project №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.

Maslyanskiy A.L. https://orcid.org/0000-0003-2427-4148
Dibrov D.A. https://orcid.org/0000-0003-3183-0464
Lila A.M. https://orcid.org/0000-0002-6068-3080
Torgashina A.V. https://orcid.org/0000-0001-8099-2107
Zotkin E.G. https://orcid.org/0000-0002-4579-2836
Samsonov M.Yu. https://orcid.org/0000-0003-2685-1623
Togizbayev G.A. https://orcid.org/0000-0002-7842-1871