Prospects for anti-B-cell therapy in immuno-inflammatory rheumatic diseases

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PROSPECTS FOR ANTI-B-CELL THERAPY IN IMMUNO-INFLAMMATORY RHEUMATIC DISEASES
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Impaired B-cell immunological tolerance plays a central role in the pathogenesis of immuno-inflammatory rheumatic diseases (IIRD). B-cells link innate and acquired immunity: they express Toll-like receptors that respond to danger signals; act as antigen-presenting cells; induce an antigen-specific immune response; determine the development of immunological memory; and synthesize a wide range of cytokines that regulate (stimulate or suppress) an immune response and inflammation. In IIRD, there are metabolic and B-cellular signaling disturbances that lead to defects in B-regulatory, T-regulatory, follicular T-helper, and dendritic cells. B-cells synthesize organ-nonspecific and organ-specific autoantibodies that are biomarkers for autoimmune diseases and play an important role in their immunopathogenesis. Anti-B-cell therapy that causes B-cell depletion in blood and target organs is effective in a wide range of IIRD. Its efficiency is determined by various mechanisms, such as suppression of pathogenic autoantibody synthesis; modulation of the function of B-cells (antigen presentation, cytokine synthesis, and costimulation), T-lymphocytes and dendritic cells. Further study of a strategy for targeted anti-B-cell therapy, mechanisms of action, and new targets is important for the progress of modern rheumatology to improve the treatment strategy of IIRD.
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Decoding immunopathogenesis, expanding diagnostic capabilities and developing new methods of treatment for immuno-inflammatory (autoimmune) rheumatic diseases (IIRDs) in humans are among the priority areas of the 21st century medicine [1, 2]. Autoimmune pathology is especially widely represented in such IIRDs as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic scleroderma (SSD), systemic vasculitis associated with the synthesis of anti-neutrophil cytoplasmic antibodies (ANCA-SV), Sjögren's syndrome/disease (SS/SD), idiopathic inflammatory myopathies (IIM), and some others. A significant breakthrough in the treatment of IIRDs was achieved in the middle of the 20th century and was associated with the widespread introduction of glucocorticoid, and later – cytotoxic therapy. However, in many patients, glucocorticoids (GC) and cytostatic therapy is not effective enough and is accompanied by the development of a wide range of adverse drug reactions (ADRs). This was a powerful incentive for the development of new approaches to treatment related to the use of genetically engineered biologic drugs (biopharmaceuticals) that block important mechanisms of IIRD pathogenesis [3, 4].

One should recall that the fundamental mechanism of autoimmunity development in IIRDs is associated with a violation of immunological tolerance to self-antigens and is a complex, multifactorial process in which, along with autoreactive B cells and plasma cells, an active role is played by T cells, other cells of the immune system, a variety of mediators that regulate the immune response and inflammation, including cytokines, growth factors, prostaglandins and leukotrienes, and, finally, signal molecules that regulate the synthesis of mediators and the function of immune system cells [5, 6]. The formation of B-cell immunological tolerance consists of several successive stages, which are defined as 'checkpoints' [7, 8]. Checkpoints 1 and 2 are localized in the bone marrow and determine the development of pre-B cells and the expression of B-cell receptors (BCRs). Interaction between the BCRs and self-antigens occurs at Checkpoint 3 (bone marrow and peripheral blood). Positive or negative selection of B cells happens at Checkpoint 4 (spleen). Somatic hypermutation of mature B cells occurs at Checkpoint 5. Checkpoints 1–3 are involved in the formation of central tolerance, while Checkpoints 4 and 5 are involved in the formation of peripheral tolerance. Tolerance regulation at Checkpoints 4 and 5 involves Toll-like receptors (TLR). Negative selection of autoreactive B cells prevents the development of autoimmunity due to several interrelated mechanisms: deletion, receptor editing, and anergia. Positive selection depends on the interaction of BCRs, BAFF (B cell activating factor), CD40, and TLR receptors. Effective immunological tolerance is based on a balance between negative and positive selection, while the development of autoimmune pathologies is associated with this balance tipping towards negative selection. In humans (and mice), several phenotypically distinct subtypes of B cells are identified: B1, B2, and marginal zone (MZ) B cells. It is believed that B1 and MZ B cells are involved in the development of innate and acquired immunity, while B2 cells are involved in the reactions of acquired immunity. A certain population of immature B cells expressing autore-

active BCRs are removed in the bone marrow due to central tolerance mechanisms. Mature B cells recirculate in the bloodstream and accumulate in the follicles of secondary lymphoid organs. After stimulation with antigens, mature B cells are transformed into *memory* B cells, short-lived or long-lived plasma cells. Memory B cells are formed within germinal centres and differ from *naive* B cells, namely, by switching from IgM synthesis to the synthesis of IgG and IgA isotype antibodies. Cross-linking of membrane IgG generates a stronger activation signal than IgM, which leads to a decrease in the activation threshold of memory B cells and the rapid formation of antibody-synthesizing plasma cells. Expression of high-affinity receptors allows memory B cells to respond to a very low dose of antigens and perform the function of antigen-presenting cells (APC). It is believed that dendritic cells (DC), which are classic APCs, perform an antigen-presenting function at an early stage of the immune response, while memory B cells perform the same function at a later (chronic) stage, thereby participating in the progression of autoimmune diseases. Memory B cells express CD27 molecule, which, when interacting with the corresponding T-cell ligand (CD70), helps differentiate activated memory B cells into plasma cells. In contrast to naive B cells, memory B cells express a peculiar profile of homing molecules (chemokines, etc.) that contribute to the optimal presentation of antigens (and self-antigens) to T cells in the context of major histocompatibility complex (MHC) class II molecules. Therefore, the ability of memory B cells to interact with T cells is a key mechanism that determines rapid formation of plasma cells, autoantibody synthesis, and modulation of the T cell function. Activation of B cells leads to clonal expansion and the formation of short-lived plasma cells in extrafollicular zones of secondary lymphoid tissues. Various subpopulations of plasma cells are found in the affected organs of IIRD patients, which differ in phenotype and differentiation stages. Looking ahead, it should be noted that some short-lived plasma cells express CD20, and therefore are sensitive to the activity of CD20 monoclonal antibodies, while long-lived plasma cells lose CD20 expression. Therefore, the depletion of B cells does not lead to suppression of the synthesis of antibodies to recall antigens (tetanus toxoid, pneumococcus) and certain types of autoantibodies characteristic of IIRDs, such as antibodies to ribonucleoprotein and Sm-antigen (SLE), Ro/SS-A and La/SS-B antibodies (SS), while other autoantibodies are sensitive or partially sensitive to this therapy.

The antigen-presenting function of B cells is associated with the synthesis of a wide range of cytokines that play an important role in the regulation of T-cell immune response, and various subpopulations of B cells, including plasmoblasts and plasma cells, synthesize a wide range of pro-inflammatory cytokines that stimulate innate and acquired immunity and thus make a significant contribution to the development of chronic inflammation (Table 1). These include, in particular, Th1-cell activating IL-12, Th17-cell activating IL-6, CD8+ cytotoxic cells activating IL-15, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which activates myeloid cells. At the same time other subpopulations of B cells (for example, B regulatory cells (Breg)) have anti-inflammatory potential, due to the production of IL-10, IL-35, TGFI, which block the Th1 – and Th17-types of immune response and myeloid cells activation.

Hyperproduction of pathogenic autoantibodies is the most characteristic manifestation of an IIRD [9]. They can induce an immune complex inflammation (SLE, RA), cause destruction of target cells (autoimmune hemolytic anemia, bullous pemphigoid, etc.), or modulate signalling pathways that regulate the functional activity of cells (Hashimoto's thyroiditis, etc.). At the same time, autoantibodies have specific anti-inflammatory effects that limit or inhibit the development of an autoimmune pathological process. The latter depends on both the isotype and glycosylation of the antibody Fc region [10].

Table 1 B-cell cytokines and cytokine regulation of B-cell function

Cytokines synthesized by B cells		Cytokines regulating the B-cell function	
Cytokine	**Effect**	**Cytokine**	**Effect**
Effector B cells		IL-7	B cell development, reorganization of immunoglobulin genes
IFNγ	Antiviral activity; support for cytotoxic activity and Th1 cell differentiation; induction of expression of MHC class I and II antigens	IL-4	B cell proliferation, switching of immunoglobulin i sotypes
IL-12	Induction of Th1 cells; activation of TR cells; DC maturation	IL-6	B cell proliferation, switching of immunoglobulin isotypes
TNFα	Activation of inflammatory cells	IL-10	Regulation of B-cell response
IL-2	Proliferation of effector T and B cells; differentiation and proliferation of NK cells; B cell growth factor and stimulation of antibody synthesis; proliferation and synthesis of cytokines by innate immune cells	IFNα	B cell proliferation, BCR sensitivity increase
IL-4	Induction and differentiation of Th2 cells; expression of MHC class II antigens on B cells	IFNβ	B cell proliferation, BCR sensitivity increase
IL-6	Induction of acute phase response; differentiation, survival, and activation of T cells; B cell differentiation, IgG, IgA, and IgM synthesis; haematopoiesis; osteoclastogenesis and bone resorption; neoangiogenesis; fibroblast proliferation and cartilage dilution	IFNγ	Inhibition/stimulation of B cell proliferation, switching of the immunoglobulin isotype
		CCL28	Recruitment of IgA + plasma cells in mucous membranes
Regulatory B cells			
IL-10	Immunosuppressive effect (T cells and APC); suppression of IgG synthesis by B cells		
TGFβ	T-regulatory and TH-17 cells induction suppression of lymphocyte and macrophage proliferation		
IL-35	Suppression of effector T cell proliferation; enhancing IL-10 synthesis and T_{reg} proliferation		

Note. NK cells – natural killer cells, IL – interleukin, TNF – tumour necrosis factor, IFN – interferon, TGF – transforming growth factor, T_{reg} – T-regulatory cells.

Currently, the role of pathological activation of B cells in the IIRD immunopathogenesis is theoretically substantiated [11–13] and anti-B cell therapy is considered as a promising direction of pharmacotherapy of these diseases [14–19]. Drugs that specifically inhibit function or cause depletion or modulation of the functional activity of various subpopulations of B cells and plasma cells have been developed and continue to be developed. These primarily include monoclonal antibodies (MAbs) to CD20 and other B-cell proteins (CD19 and CD22); MAbs that block the activity of cytokines that regulate B cell survival and functioning (BAFF/APRILL – B cell activating factor/a proliferation-inducing ligand), low-molecular proteasome inhibitors that specifically eliminate plasma cells, and others (Table 2). Moreover, anti-(pan)-B-cell therapy is very effective not only in classic B-cell autoimmune diseases, but also in diseases in which T lymphocytes play a leading role, such as RA and multiple sclerosis. The results of clinical use of these drugs in patients suffering from autoimmune diseases enabled us to obtain new data concerning the mechanisms of autoimmunity development and the immune system regulation in general. It should be borne in mind that the human body synthesizes the so-called 'natural' autoantibodies, which have protective activity, and in some cases, anti-B-cell therapy leads to a relapse of autoimmune pathology. These data confirm the complexity of autoimmunity B-cell regulation mechanisms.

In recent years, significant attention has been paid to B_{reg} that have the ability to suppress the development of autoimmune inflammation and maintain peripheral tolerance [20]. B_{reg} phenotypes, which include, among others, a subpopulation of CD24(high)CD27+ B cells and CD24(high)CD38(high) transitional B cells were characterized. Suppression mechanisms include inhibition of CD4+ T cell proliferation, induction and expansion of T_{reg}, inhibition of Th1 cell differentiation, and suppression of monocyte activation. A decrease in B_{reg} suppressor activity was found in SLE, immune thrombocytopenia, RA, ANCA-SV, and bullous pemphigoid. It is believed that the lack of efficacy and ADR development in anti-B-cell therapy in autoimmune diseases is associated with their ability to eliminate not only pathogenic subpopulations of B cells, but also B_{reg}.

The vast majority of studies concerning the efficacy and safety of anti-B-cell therapy are related to the study of RTM [21], which essentially is chimeric mAbs to the CD20-antigen of B cells. The choice of a CD20 molecule as a target for RTM is related to the peculiarities of differentiation of B cells that go through several successive stages during maturation, each of which is characterized by the expression of certain membrane molecules. CD20 expression is observed on the membrane of early and mature B cells, but not in stem cells, early pre-B and plasma cells. Therefore the use of RTM does not cancel the regeneration of new B cells neither it affects the synthesis of normal antibodies by plasma cells. In addition, CD20 is not released from the B-cell membrane and is absent in a circulating (soluble) form that could potentially interfere with the interaction of anti-CD20 antibodies with B cells. The physiological value of CD20 is to maintain the intracellular Ca^{2+} concentration (Ca^{2+} influx through the cell membrane), which regulates B cell activation. After binding to CD20, RTM induces a

Table 2 Anti-B-cell drugs in IIRD treatment

Drug	Disease		
	RA	SLE	Other
Anti-CD20 mAbs			
RTM (Rituximab) – MabThera® – Acellbia®	Market authorization	Off-label use	Market authorization: granulomatosis with polyangiitis microscopic polyangiitis bullous pemphigoid Off-label use SSD SS inflammatory idiopathic myopathies antiphospholipid syndrome IgG4-associated disease HCV-associated cryoglobulinemic vasculitis
Ocrelizumab, Ocrevus	RCT termination	RCT termination	Market authorization multiple sclerosis
Veltuzumab, Veltucyn	RCT termination		Idiopathic thrombocytopenic purpura (Phase I/II)
Obinutuzumab, Cazyva		Phase II	Market authorization chronic lymphocytic leukaemia non-Hodgkin's lymphoma
Ofatumumab, Arzerra			Market authorization chronic lymphocytic leukaemia Multiple sclerosis (Phase II)
Ocaratuzumab		Phase I	
SBI-087	RCT termination	RCT termination	
Anti-CD19 mAbs			
Inebilizumab			
MDX-1342	Phase I		Multiple sclerosis – Phase I/II Optical neuromyelitis – Phase II/III Systemic scleroderma – Phase I
XmAB5871	Phase II	Phase II	
Anti-BAFF mAbs			
Belimumab, Benlysta	RCT termination	Market authorization	ANCA-associated vasculitis – Phase III Inflammatory myopathies – Phase II/III Membranous glomerulonephritis – Phase II Myasthenia gravis – Phase II SS – Phase II SSD – Phase II Kidney transplant rejection – Phase II
Tabalumab	RCT termination	RCT termination	Multiple sclerosis – RCT termination
Blisibimod		Phase III	IgA nephropathy – Phase II
TACI: IgG Fc-recombinant protein			
Atacicept	RCT termination	Phase III	Multiple sclerosis – RCT termination IgA nephropathy – Phase II
RCT 18	Phase III	Phase II	

Note. RTM – Rituximab, RCT – randomized placebo-controlled trial

complement-dependent cell cytotoxicity (CSC) reaction due to clustering of the Fc region of antibodies. Regardless of the type of autoimmune pathology, RTM administration leads to almost complete (>90%) depletion of B cells. However, the clinical efficacy of RTM therapy in various IIRDs (and in individual patients) differs significantly. After discontinuation of RTM therapy, the level of B cells recovers within 6–10 months, the speed and intensity of this process varies substantially among different patients and in various autoimmune diseases. The high efficacy of RTM treatment of lymphoproliferative and autoimmune diseases was instrumental in the development of the second generation of anti-CD20 antibodies, which, in contrast to RTM, are humanized or completely human, have more powerful effector functions and low immunogenicity [22]. To recap, B cells anti-CD20 antibodies are conditionally divided into two main categories by their mechanism of depletion: type I and type II. Type I antibodies (RTM, Ocrelizumab, and Ofatumumab) react with CD20 in lipid rafts (microdomains of the cell plasma membrane enriched with glycosphingolipids and cholesterol) and, by binding to the C1q component of the complement, induce CSC reaction and, to a lesser extent, antibody-dependent cell cytotoxicity. In contrast, type II antibodies interact with a CD20 region that is outside the lipid raft, poorly binds to C1q, but is a strong inducer of cell death associated with CD20-dependent B cell signalling. It is noteworthy that Ocrelizumab and Ofatumumab have demonstrated efficacy in patients with SLE who develop allergic reactions or resistance to RTM [23, 24].

Other important B cell targets are BAFF/APRIL. The development of anti-BAFF mAbs – Belimumab (BLM) – is associated with the progress of fundamental research in the field of SLE immunopathology. The discovery of the key role of B cells in the SLE immunopathogenesis has attracted attention to the study of B-cell cytokines as possible targets for therapeutic effects. Let us recall that BASF, also known as BLyS (B lymphocyte stimulator), is an important component of regulating B cell function, proliferation, and differentiation [25, 26]. BLM prevents the interaction of BAFF with cellular receptors of autoreactive transitional and naive B cells, which leads to the suppression of B-cell hyperreactivity characteristic of SLE, in particular, the synthesis of autoantibodies, a decrease in the survival of B cells localized in the growth centres of lymphoid organs, differentiation of memory B-cells into autoantibody-producing cells, and the synthesis of pro-inflammatory cytokines (IL-21, IL-17 and others), which play an important role in SLE immunopathogenesis.

Rheumatoid arthritis

The clinical and immunological effects of RTM therapy and its place in the treatment of RA are discussed in detail in our previous publications [27, 28] and reviews by other authors [29]. Currently, RTM is considered as an effective drug for RA treatment, included in the international (EULAR – European Antirheumatic League) [30] and Russian recommendations [31] for the treatment of this disease. The clinical efficacy of RTM is associated with the detection of antibodies to cyclic citrullinated proteins (anti-CCP) and rheumatoid factors (RF) [32, 33]. The significance of other serum and cellular biomarkers for predicting RTM efficacy is discussed in our previous publication [34] and reviews by other authors [35]. Despite the proven role of anti-CCP and RF in RA immunopathogenesis, suppression of the synthesis of these antibodies does not allow to explain the effectiveness of RTM in RA treatment, since the rate and intensity of the decrease in these AB titres vary widely, are not observed in all patients, and do not correlate with the efficacy of the therapy. It was found that the clinical effect of RTM is associated with a low basal level of IFNγ, correlates with a decrease in the level of CD4+ T cells in peripheral blood, some of which may be targets for RTM, since they express CD20. Since, as already noted, B cells are involved in the activation of T cells, especially at the stage of chronic inflammation; it can be assumed that B cell depletion leads to a weaker formation, clonal expansion and function of T cells that regulate the B-cell immune response. RTM treatment is accompanied by long-term repopulation of naive B cells with a new immune repertoire, compared to B cells subjected to initial depletion, and a slower repopulation of memory B cells. It is believed that this can lead to suppression of B cell maturation, which in turn blocks the switching from the synthesis of natural (‘protective?’) IgM-antibodies to ‘pathogenic’ IgG-autoantibodies. Thus, in autoimmune diseases, the immunosuppressive effect of B-cell depletion can be actualized by two reciprocal mechanisms: elimination of autoreactive B cells synthesizing 'pathogenic' IgG-autoantibodies and B_{reg} formation. Another mechanism of RTM activity is associated with its modulation of autoantibody glycosylation. Let us recall that the development of autoimmune diseases is characterized by the predominant synthesis of inflammatory IgG-autoantibodies, characterized by low glycosylation of Fc- and, possibly, Fab-fragments. Reduced glycosylation of total IgG and IgG of anti-CCP is associated with RA development in patients at risk of developing the disease (inflammatory arthralgia), and correlates with the activity of the disease [36]. It was found that activation of the IL-17/IL-23 axis has pathogenetic significance primarily in the early stages of RA, during the formation of the ‘pro-inflammatory’ potential of the anti-CCP [36, 37]. According to experimental studies (collagen arthritis), IL-23 induces the activation of Th17 cells that synthesize IL-21 and IL-22 and, accumulating in the growth centres of secondary lymphoid organs, suppress the expression of β-galactoside-α2,6-Sialyltransferase (St6gal1) in plasmoblasts and plasma cells, which induces the formation of a 'pro-inflammatory' glycosylation profile of anti-CCP [38]. There is evidence that RTM reduces the expression of Th17-cell transcription factor – retinoic acid related orphan receptor γt, IL-22 and a number of Th17-positive cells in the synovial tissue of RA patients, which correlates with the clinical efficacy of therapy[39]. According to other studies, IL 17+ DC and CD4+ Th17 cells express CD20 at least in salivary gland tissue in SD patients [40]. One can assume that by suppressing the synthesis of Th1 (IFNγ) and Th17 (IL-17, IL-21, IL-22) cytokines, RTM has the ability to shift the balance towards the synthesis of low-glycosylated anti-inflammatory autoantibodies.

Data were obtained that create theoretical prerequisites for the use of RTM for the primary prevention of RA in patients with a high risk of this disease development – in the so-called 'clinically suspected arthralgia' [41, 42]. According to the PRAIRI (Prevention of clinically manifest Rheumatoid ArthrItis by B Cell DiRected Therapy In the Earliest Phase of the Disease) multicentre RCT, which included patients with arthralgia who tested positive for anti-CCP and RF, a single RTM infusion significantly slows the development of RA [43]. In general, the data presented above justify the use of RTM for the purpose of primary prevention of autoimmune pathology development in patients with high risk of RA, and possibly other IIRDs.

Systemic vasculitides

Systemic vasculitides associated with antineutrophilic cytoplasmic antibodies (ANCA-SV) is a heterogeneous group of severe systemic autoimmune diseases, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [44]. RTM has been authorized for the treatment of GPA and MPA [45]. The following factors are prerequisites for the use of RTM in ANCA-SV: B-cell activation is associated with the activity of vasculitis; the effectiveness of Cyclophosphamide (CP) in ANCA-SV is largely determined by anti-B-cell effects; anti-B-cell therapy suppresses the synthesis of pathogenic ANCA [13, 46].

Over the past 10 years, several randomized controlled trials (RCTs; Table 3) and open clinical studies have been conducted, which demonstrated RTM efficacy as a component of induction and/or maintenance therapy in patients with insufficient efficacy of GCs and immunosuppressive drugs (primarily CP) in patients with ANCA-SV [47].

The multicentre RCT RAVE (the Rituximab Versus Cyclophosphamide for AAV) included patients with recurrent or newly diagnosed ANCA-SV [48–50]. All patients were administered high doses of GCs with their abrupt withdrawal and RTM (375 mg/m^2 4 infusions at 1 week intervals) or CP (2 mg/kg orally), followed by maintenance therapy with Azathioprine (AZA). RTM is not inferior to CP in terms of remission induction. The incidence of remission in RTM treatment (64%) was higher than that of CP (53%; p=0.09), especially in the subgroup of patients with a relapsing course of disease (66% vs. 44%; p=0.01) and in patients who tested positive for Anti-proteinase 3 (anti-PR3) antibodies. It is noteworthy that an increase in anti-PR3 titres is associated with an increased risk of the disease relapse, primarily in patients with kidney damage and alveolar haemorrhages [51]. According to the data of the open phase of this study, the course of RTM therapy was not inferior in terms of efficacy to standard immunosuppressive therapy (AZA) in maintaining the remission [52]. The RITUXVAS (Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis) [53, 54] study showed that RTM (375 mg/m^2 4 infusions at 1 week intervals) in combination with two courses of CP pulse therapy followed by low-dose GC therapy (5 mg/day) is not superior in terms of efficacy to standard intravenous CP therapy regarding the frequency of remission induction (renal and pulmonary) in 12 months (76% vs. 82%; p=0.77). The frequency of infectious complications in the compared groups did not differ. These data suggest that RTM may be an alternative to CP for inducing remission in patients with severe ANCA-SV, including with kidney damage. When using standard therapy, most patients achieve remission within 3–6 months, but more than half of them subsequently develop a relapse, the risk of which is higher in GPA than in MPA and when anti-PR3 is detected [55]. A single course of RTM can induce remission in most patients with ANCA-SV, but does not reduce the risk of relapse 54]. At the end of maintenance therapy, the frequency of relapse reaches 40% after the last RTM infusion (in 34.4 months on average) [56]. Although B cell repopulation and an increase in ANCA titres precede the relapse, the clinical significance of these biomarkers is not fully clear. In contrast to SLE, in which the development of exacerbations is associated with the repopulation of CB27+ memory B cells, in ANCA-SV, a decrease in the level of CD5+ B regulatory cells is observed during this period [57]. In the absence of available predictive biomarkers, data from the MAINRITSAN RCT [58, 59] are of particular interest. In this RCT patients who received CP induction therapy were given low doses of RTM (2 doses of 500 mg in the first 6 months, and then 500 mg every 6 months) or AZA as a maintenance therapy. The frequency of exacerbations (within 28 months) in the RTM group (5%) was significantly lower than in the AZA group (29%; p=0.002), and the frequency of ADR was similar. In the course of long-term follow-up of patients, it was shown that RTM is superior to AZA in terms of maintaining remission for 5 years of the follow-up (57.9% and 37.2%; p=0.012). Currently, the RATIZAREM (Rituximab Vasculitis Maintenance) study is underway to compare the efficacy of RTM maintenance therapy (1 g every 4 months) and AZA in patients who achieved remission through RTM induction therapy [60]. The results of the MAINRITSAN2 study, which evaluated the optimal time interval for RTM administration to maintain remission based on the analysis of biomarkers (B cell repopulation or an increase in ANCA titres), are considered important [61]. It was found that in the group of patients who were prescribed RTM every 6 months, there was a lower (although not completely) frequency of relapse (9.9%) than in the group of patients whose RTM administration was based on the changes in biomarkers (17.3%; p=0.22). The results of a retrospective analysis of patients with ANCA-SV who received RTM maintenance therapy at fixed intervals for 2 years indicate the efficacy of this approach to maintenance therapy [62]. In a series of open clinical studies,

Table 3 Results of controlled studies of RTM therapy in ANCA-SV

Study	RAVE [48-50]	RITUXIVAS [51, 52]	MAINRITSAN [53, 54]
Number of patients (randomization)	297 (1:1)	44 (3:1)	118 (1:1)
GPA/MPA/RLV, %	76/24/0	50/36/0	76/20/4
Kidney damage, %	66	100	70
First flare, %	49	100	70
Treatment			
induction (all – PRED)	RTM 375 mg/m^2 (Day 0, 7, 14, 21) vs. CP p/o.	RTM 375 mg/m^2 (Day 0, 7, 14, 21) + CP i/v (Day 0 and 14) vs. CP i/v + PRED	CP i/v
maintenance therapy	RTM group w/o maintenance therapy vs. AZA	RTM group w/o maintenance therapy vs. AZA	RTM 500 mg (Day 0, 14, Month 6, 12, 18)
Outcome	Remission w/o GC: 64% (RTM) vs. 54% (CP – AZA) in 6 months; 39% and 33% in 18 months RTM is better in patients with recurrent course of the disease (p=0.01)	Remission in 12 months: 76 (RTM) 82% (CP – AZA)	Major relapse in 28 months: 5% (RTM) and 29% (AZA) (p=0.002)

Note. RAVE – Rituximab for ANCA-Associated Vasculitis, RITUXIVAS – Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis, MAINRITSAN – Maintenance in Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis; PRED – prednisolone, p/o – orally, i/v – intravenously.

the efficacy of RTM has been demonstrated in relation to organ manifestations of ANCA-SV, including necrotizing scleritis [63], pulmonary granulomas [64], EGPA [65–68], in patients resistant to CP therapy and other immunosuppressive drugs [69–76], as well as combined induction therapy of RTM and CP [77]. It is important that during RTM therapy, the concentration of 'pathogenic' IgG ANCA decreases to a greater extent than the level of general IgG [78].

In our own experience (Table 4–6) of treating 58 patients with GPA and 35 patients with MPA, who all had high activity of the disease (32% with BVAS ⩾20 points), severe organ lesions [in 24% – glomerulonephritis (GN) of rapid progression], resistance to standard therapy (in 39% of cases refractory course of ANCA-SV was observed), contraindications for cytostatic therapy or their intolerance (in 27%), the use of RTM in most cases allowed to achieve remission (93%), including GC discontinuation in 10 patients (11%) [79, 80]. The number of patients receiving cytostatics decreased to 43%, mainly Mycophenolate mofetil (MMF) and AZA. Treatment with repeated courses of RTM, which were prescribed to 82% of patients (usually in a

Table 4 Characteristics of IIRD patients (n=511) treated with RTM

Parameters	ANCA-SV		SLE	SSD	SS/SD	IgG4-AD	CGV
	GPA and MPA	EGPA					
Number of patients	103		167	90	100	34	21
	93 (58 – GPA, 35 – MPA)	10 (4 – ANCA+, 6 – ANCA-)					
Women, %	56	90	92	75	97	60	52
Age, years*	45 (16–77)	50 (24–71)	41 (18–52)	47 (17–71)	42±12.2	47.4±15.9	53,6±29
Illness duration, months*	14 (2–288)	11 (1–180)	18 (2–47)	70 (7–264)	90 (36–168)	24 (6–60)	72 (3–96)

Note. * – the data are given in the following format: median, in brackets – minimum – maximum or M±σ (here and in Table 5), CGV – cryoglobulinemic vasculitis

Table 5 Clinical efficacy of RTM in patients with IIRDs (n=511)

Parameters	ANCA-SV		SLE	SSD	SS/SD	IgG4-AD	CGV
	GPA and MPA	EGPA					
Number of patients	103		167	90	100	34	21
	93	10					
RTM courses, proportion of patients, %:							
One	18	–	58	14	–	6	10
Two	17	20	24	13	–	–	14
Three and more	65	80	18	73	100	94	76
The average total dose of RTM during the period of observation, g*	3 (0.5–8)	3 (1.5–5.5)	2.4 (1.8±0.8)	2.9 (0.5–6)	5.5±1.5	4±1.5	4.7±3.8
Duration of follow-up after the first course of RTM, months*	37 (1–96)	32 (9–90)	38 (12–67)	27 (12–42)	58 (24–96)	25 (3–60)	52 (6–108)
Clinical response, number of patients, %:							
Complete (good)	93	90	49	70	92.5	77	71
Incomplete	6	10	32	24	6.5	23	29
No response	1	0	19	6	1	–	–
Average dose of GC, mg/day*:							
before RTM treatment	30 (5–60)	20 (7,5–50)	28 (15–40)	12 (0–25)	7,5 (0–40)	10 (2,5–40)	4,4 (0–24)
after RTM treatment	5 (0–10)	7,5 (5–10)	7,5 (5–15)	9 (0–15)	1,25	0,5	1,5 (0–4)
Immunosuppressants, number of patients, %:							
before RTM treatment	72	90	65	43	44	40	38
after RTM treatment	43	70	46	50	8	10	5

Table 6 ADRs on RTM therapy of IIRD

Complications	ANCA-SV (n=103)		SLE (n=167)	SSD (n=90)	SS/SD (n=100)	IgG4-AD (n=34)	CGV (n=21)
	GPA and MPA (n=93)	EGPA (n=10)					
Infusion reactions	8 (9)	2 (20)	7 (4)	2 (2)	10 (10)	1 (3)	5 (24)
including severe, n (%)	0	1 (10) – bronchospasm	1 (0.6)	1 (1) – bronchospasm	1 (1)	–	–
Total patients with severe ADR, n (%)	24 (26)	4 (40)	23 (14)				
including serious infections	10 (11)	1 (10)	17 (10)	2 (2)	5 (5)	1 (3)	1 (5)
Other serious ADRs, n (%)	4 (4) – thrombosis 9 (10) – neutropenia	1 (10) – thrombosis 2 (20) – neutropenia	5 (3) – neutropenia				
Number of deaths during the follow-up period, n (%)	10 (11)	–	8 (5)	5 (6)	2 (2)	–	3 (14)

reduced dose of 500 mg at intervals of 4–12 months), contributed to a stable complete depletion of circulating CD20+ B cells and long-term clinical and immunological remission. The incidence of ANCA-SV relapses after remission induced by RTM was 11%. Despite the severe and / or complicated course of ANCA-SV in most cases, the overall mortality rate for the follow-up period of 37 (1–96) months was 11%, with rapidly progressing GN in 27% of cases. The use of RTM was highly effective in all 10 EGPA patients, including three (30%) with high disease activity (BVAS >20 points), six (60%) with severe polyneuropathy, and two (20%) with severe heart failure. A complete (good) response was observed in 9 out of 10 cases of EGPA, both in ANCA-associated and ANCA-negative variants of the disease, and there were no cases of fatal outcome. In 60% of cases (in 6 out of 10 patients), complete EGPA remission was found on a reduction in the dose of Prednisolone to ⩽7.5 mg/day. The incidence of EGPA relapses after remission induced by RTM was 30%.

In a series of open studies and clinical observations, the efficacy of RTM has been demonstrated in patients with severe Henoch-Schönlein purpura, kidney damage, in patients resistant to GC and CP, in children and adults [81–88].

Numerous studies are dedicated to the research of RTM efficacy in HCV-associated cryoglobulinemic vasculitis (HCV-CGV) [89–98]. D. Roccatello et al. [99] summarized the data of the main studies (16 open and 3 RCTs) on the efficacy and safety of RTM in CGV treatment, which included more than 400 patients (one third of patients received RTM monotherapy, while the rest received RTM in combination with other immunosuppressive or antiviral drugs). The main indications for RTM were skin lesions (vasculitis, purpura, or ulcers – 62%), neuropathy (58%), and kidney damage (33%). Complete remission was observed in 68% of patients, partial remission in 14% of patients, and no effect was observed in 10% of patients. Among patients with kidney damage, complete remission was observed in 57% of patients, partial remission – in 29%, and no effect was observed in 40% of patients. RCT of M.C. Sneller et al. [89] included 24 HCV-CGV patients with insufficient efficacy of standard immunosuppressive and antiviral therapy. After 6 months, remission development was observed in 10 (83.3%) patients receiving RTM (375 mg/m^2, weekly, for 4 weeks), and only one patient (8%) in the control group. During the next 6 months, 6 out of 10 patients in the RTM group remained in remission, and 4 developed a relapse that was successfully controlled in a second course of RTM. The steroid sparing effect of RTM therapy was noted [89, 92]. With respect to inducing remission and reducing the frequency of relapses RTM therapy was more effective in patients who did not receive prior immunosuppressive therapy [89]. The use of RTM was not accompanied by activation of viral infection [89, 92]. According to F. Dammacco et al. [94], HCV-CGV treatment using the PIRR Protocol (PEGylated Interferon, Ribavirin, Rituximab) as a starting therapy is more effective against kidney damage, cancer, and neuropathy than therapy with PEGylated IFNγ (PEG-IFN) and Ribavirin. Complete remission occurred in 54.5% of patients treated according to the PIRR Protocol, and in 33.3% of patients in the antiviral therapy group. RTM efficacy is higher when combined with PEG-IFN and Ribavirin [90, 93, 94]. The frequency of virological remission in the PIRR group of patients was 55%. There is evidence of successful use of RTM in patients with severe forms of HCV-CGV that are refractory to standard therapy and comorbid diseases such as liver cirrhosis and lymphoma [95–100].

Knowing by my own experience (see Tables 3 and 4) of the use of RTM in 21 patients with HCV, among which 81% had genotype I of HCV and 38% had liver cirrhosis, the treatment was effective in all cases, with 71% of patients having a complete (good) response and 29% demonstrating an improvement. The frequency of fatal outcomes was 14% for the duration of the follow-up of 52 (6–108) months; in all three cases death occurred due to decompensation of liver cirrhosis. It should be noted that the CGV group was characterized by a severe course with high disease activity; in all cases there was purpura; in 81% – peripheral polyneuropathy (in 38% – flaccid peripheral para/tetraparesis against the background of severe axonal-demyelinating polyneuropathy); in 43% – GN (in 8 of 9 cases it was confirmed morphologically); and in 33% – ulcerative necrotic skin lesions, often severe, up to gangrene of all fingers. Prior to RTM administration, 29% of patients received antiviral IFN therapy (five of them – PEG-IFN) without achieving a stable virological response with an exacerbation of systemic vasculitis in 5 out of 6 cases. In between RTM courses, 24% of patients received antiviral therapy with an improvement in all cases. In one patient, RTM treatment was discontinued after completion of the antiviral therapy with the achievement of HCV-CGV remission.

Systemic lupus erythematosus

SLE is a systemic non-organ-specific autoimmune disease of unknown etiology characterized by hyperproduction of organ-specific autoantibodies to various components of the cell nucleus with the development of immuno-inflammatory damage to tissues and internal organs [101, 102], which is pathogenetically associated with pathological activation of B cells [103–107].

RTM is widely and successfully used in clinical practice for SLE treatment [108] and is included in international [109–113] and Russian [31] recommendations for the treatment of this disease. At the same time, the results of RCTs are contradictory. In two RCTs: the EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab) [114, 115], which included patients with active SLE without kidney lesions, and LUNAR (Lupus Nephritis Assessment with Rituximab) [116] with lupus nephritis (LN), primary endpoints reflecting the efficacy of therapy were not reached (Table 7). According to experts, the negative results of these RCTs are associated with imperfect protocols (the nature of concomitant therapy, its duration, heterogeneity of patients), indices used to assess the effect of treatment, and some other factors [117]. The improvement of SLE immunological markers (normalization of C3- and C4-components of the complement, reduction of anti-DNA titres) and a decrease in the need for immunosuppressive therapy indicate the efficacy of RTM. It is noteworthy that, according to a retrospective analysis of the LUNAR study, the efficacy of RTM therapy was associated with complete depletion of B cells in peripheral blood [118].

The efficacy of RTM therapy has been established in patients with severe SLE (see Table 7), who are resistant to standard GC and immunosuppressant therapy: LN, haematological disorders (haemolytic anaemia, immune thrombocytopenia) [139–145], neuropsychic manifestations [146, 147], antiphospholipid syndrome (APS) [131, 148], including catastrophic [149], macrophage activation syndrome [101], pulmonary haemorrhages [148, 151, 152], lupus myocarditis [148], severe skin lesions [153]. Against the background of RTM treatment, there was a rapid improvement in quality of life indicators (SF-36 and FACIT-Fatigue; p=0.031 and p=0.007, respective-

Table 7 Results of main clinical studies of RTM in SLE treatment

Authors	Study design	Number of patients	Treatment regimen	Key findings
J.T. Merril et al. [114]	RCT (2:1)	257 (active SLE)	RTM 1 g or PL; Day 1, 15, 168, 182	Extrarenal manifestations (p>0.05)
B.H. Rovin et al. [116]	RCT (1:1)	144 (active SLE)	RTM 1 g or PL; Day 1, 15, 168, 182	Kidney lesions (p>0.05) Reduced level of anti-dsDNA and an increase of C3/C4-complement components
M.J. Leandro et al. [119]	Concurrent open	24 (active SLE)	RTM 1 g, CP, MP	BILAG scores reduction, anti-dsDNA, C3-component increase
T.Y. Lu et al. [120]	Nonconcurrent	50	Same	BILAG: remission – 42%, partial remission – 47%, anti-dsDNA level reduction and complement C3-component increase
C. Diaz-Lagares et al. [121]	Nonconcurrent multicentre, registration	165 (LN)	RTM + GC, CP, MMF	In 6 and 12 months: remission – 42%, partial remission – 47%, no response – 33%
M.B. Condon et al. [122]	Cohort Concurrent	50 (LN)	RTM 1g + MP 500 mg once every 2 weeks	In 52 weeks: response – 90%, complete laboratory remission – 52%, 22 patients had a relapse in 61.6 (2–112) weeks
M. Witt et al. [123]	Nonconcurrent multicentre, registration	85 (active SLE)	RTM: 1g once every 2 weeks Re-treatment	Complete response – 46.8%, Partial response – 34.2%, No response – 19.0% SLEDAI – decrease from 12.2 to 3.3 Improvement in clinical manifestations and immunological indicators
D. Albert et al. [124]	Concurrent Multicentre	24 (mildly active SLE without immunosuppressive drugs)	RTM 1g once every 2 weeks	SLEDAI improvement (52 weeks) in 70%
C. Lindholm et al. [125]	Nonconcurrent Single centre	26 (nephritis, haematological disorders), refractory to standard therapy	RTM 375 mg/m^2 4 infusions at a 1 week interval	Complete or partial response in 11 out of 17 patients with LN. Normalization of haematological indicators in 5 out of 10 patients with cytopenia
M. Ramos-Casals et al. [126]	Multicentre, registration	107 (refractory to standard therapy)	RTM 1g once every 2 weeks or 375 mg/m^2 (4 infusions at a 1 week interval)	Complete response – 47%, Partial response – 34%, No effect – 24%
E.M. Vital et al. [127]	Open single centre	39 (active SLE)	RTM 1g once every 2 weeks	Complete response – 51%, Partial response – 31%, Relapse in 6-18 months – 50%
A. Fernandez-Nebro et al. [128]	Nonconcurrent Multicentre	116 (active SLE)	Various regimens of RTM administration	In 6 months: Complete response – 17%, Partial response – 44%, Response to therapy (total) – 77%, relapse – 38%
B. Terrier et al. [129]	Observational concurrent	136 (active SLE)	Various regimens of RTM administration	Improvement in SELENA-SLEDAI – 71%, Relapse – 41%, Good response with repeated administration of RTM – 1%
L.F. Pinto et al. [130]	Concurrent Observational Multicentre	42 (active SLE, refractory to standard therapy)	RTM 1g once every 2 weeks	In 12 months (proteinuria): complete remission – 28%, partial remission – 36% In 12 months (creatinine): complete remission – 12.5%, partial remission – 33% Steroid sparing effect
C.R. Wang et al. [131].	Nonconcurrent single centre	63 (SLE with APS), RTM – 6 patients	RTM 1 g once in 2 weeks	No thrombosis relapses, reduced SLE activity (SLEDAI-2K)
E.M. McCarthy et al. [132]	Registration BILAGBR	261 (active SLE)	RTM 1 g once in 2 weeks	In 6 months - improvement in BILAG (p<0.0001) and SLEDAI-2K (p<0.001). Overall effect in 49% of patients
B. Gracia-Tello et al. [133]	Concurrent	16 (early SLE)	RTM 1 g once in 2 weeks	Tendency to decrease the frequency of relapses, decrease in anti-dsDNA titres, ESR, increase in the concentration of the C3 component of the complement. Decrease in the cumulative dose of GC (p=0.01)
N. Chavarot et al. [134]	Nonconcurrent multicentre	15 (membranous LN)	RTM 1 g once in 2 weeks Low dosages of GCs and HC	Remission 87%
R. Aguiar et al. [135]	Nonconcurrent single centre	115	Various regiments of RTM administration	Complete remission – 40% Partial remission – 36.5%: Increase in the level of C3 component of complement – 25%, decrease in anti-dsDNA – 33.5%

Continuing of table 7

Authors	Study design	Number of patients	Treatment regimen	Key findings
S. Iwata et al. [136]	Nonconcurrent single centre	63	RTM 500 mg or 1 g 2–4 cycles	Complete response – 60% Partial response – 25% No response – 8.8%
А.В. Торгашина et al. [137]	Concurrent single centre	18 (LN)	Various regiments of RTM administration	In 12 months: overall efficacy in 68%, complete remission in 7 patients, SLEDAI-2K reduction (p<0.05), decrease in the index of morphological activity during kidney biopsy (p=0.027)
M.E. Tsanyan et al. [138]	Concurrent single centre	97 (active SLE) 6 years of follow-up	RTM (various regimens)	Therapy efficacy – 87%: Complete remission – 56% Partial remission – 28%:

Note. HC – hydroxychloroquine; dsDNA – double strand DNA; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; BILAG – British Isles Lupus Assessment Group Index.

ly) after 3 months, EQ-5D after 6 months (p=0.016) and HAQ-DI after 3 months (p=0.033) [154]. In a series of studies, high efficacy of RTM therapy in juvenile SLE has been demonstrated [155–157].

Meta-analysis data [158] confirm the efficacy of RTM therapy in SLE in general and in LN, the most severe and prognostically unfavourable complication of SLE. The meta-analysis included 22 studies evaluating the efficacy of RTM in 866 patients with refractory SLE, 10 studies targeting 223 patients with refractory LN, and one study that included 10 patients with neuropsychic manifestations of SLE [119, 120, 123–130, 138, 159–177]. Overall, the general, complete or partial effect occurred in 72; 46 and 32% of patients, respectively; a significant decrease in SLE activity according to the SLEDA (Systemic Lupus Erythematosus Disease Activity) index and BILAG (British Isles Lupus Activity Group) were noted with p<0.0001 in both cases, GC doses (p<0.001) were administered to patients with SLE both without LN and with LN, and proteinuria (p=0.07) was noted in LN patients.

Given the variability in the clinical efficacy of RTM in SLE treatment, the study of clinical, genetic and immunological factors that allow predicting the efficacy of therapy may be of great importance [178]. Meta-analysis data which included 16 studies [114, 115, 125–128, 159, 179–187] evidence that their quality was not good enough to allow to reveal significant correlation between the response to RTM treatment, clinical phenotype, severity of disease, basal antibody levels to extractable nuclear antigen, anti-Ro/SS-A, and gene polymorphism of proinflammatory cytokines. Thus, the question of personalized RTM therapy for SLE remains open.

At the same time, there is evidence of an association between the clinical efficacy of RTM therapy in SLE treatment and the development of complete B cell depletion according to highly sensitive cytofluorimetry [23, 127]. It is noteworthy that second-generation anti-B cell drugs (Ocrelizumab and Ofatumumab) [23, 24] are very effective in patients with SLE who have RTM resistance associated with the absence of B cell depletion (or the development of allergic reactions).

Our own experience of RTM administration in SLE treatment encompassed 167 patients (see Table 3 and 4), of which 49% had LN (85% with proteinuria exceeding 0.5 g/l), 65% had a decrease in the concentration of the C3 component of the complement, SLEDAI-2K median was 19 (12–24) points, despite the use of immunosuppressants before the administration of RTM in 65% of cases. The use of RTM allowed for a complete (good) response in 49% of SLE cases, and an incomplete response in 32% of patients. At the same time, the mortality rate was 5% in the follow-up period of 38 (12–67) months.

Antiphospholipid syndrome

The use of RTM in APS, which is a set of clinical and laboratory symptoms characterized by venous and arterial thrombosis, pregnancy pathology, pathogenically associated with the synthesis of antiphospholipid antibodies (APLA), is worthy of interest [188]. D. Kumar and R.A.S. Roubey [189] summarized the results of RTM therapy in 21 patients with APS. Venous thrombosis was observed in 18 patients, arterial thrombosis in 9 patients, including transient ischemic attacks, and thrombocytopenia in 11 patients. In 5 patients, the development of catastrophic APS was noted. Against the background of RTM therapy, a clinical response was observed in 19 of 21 patients. Two patients had a relapse: venous thrombosis in one case, and thrombocytopenia in the other. No response was observed in only two patients, one of whom (with catastrophic APS) died. All patients (n=12) showed a decrease in APLA titres over time. It is noteworthy that in patients with thrombocytopenia, a decrease in APLA titres during RTM therapy correlated with normalization of platelet levels. According to the Phase II concurrent pilot study RITAPS (RITuximab in APS) (12 months duration) [190], which included 12 patients, the use of RTM allows to control some of the so-called 'non-critical' manifestations of APS, primarily haematological (thrombocytopenia), skin ulcers, despite the lack of changes in APLA titres [191]. There are data on RTM efficacy in treating the so-called catastrophic APS [192, 193]. Among 20 patients treated with RTM, 16 (80%) recovered, but 4 patients died. Similar data on RTM efficacy in patients with catastrophic APS (primary or combined with SLE) are provided by other researchers [131, 148, 149, 194–196].

Systemic scleroderma

B cells play an important role in the immunopathogenesis of SSD [11, 197], which creates theoretical prerequisites for the use of anti-B-cell therapy for SSD treatment. According to early studies, RTM suppresses the development of cutaneous fibrosis in patients with a graft-versus-host reaction [198]. Further data were obtained on the efficacy of RTM in relation to lung damage, skin fibrosis, as well as arthritis and calcinosis in SSD (Table 8). The materials of a retrospective analysis of 53 patients receiving RTM therapy showed a significant improvement in mRSS after 6 months (p=0.007) and after 12 months (p=0.008), and an increase in FVC (p=0.0001), and DLCO (p=004) after 12 months [210].

Table 8 Results of main clinical studies of RTM in SSD treatment

Authors	Study design	Number of patients	Treatment regimen	Key findings
R. Lafyatis et al. [199]	Open observational	15 (diffuse SSD)	RTM 1 g once in 2 weeks	No mRSS changes (6 months) PFT stabilization, internal organ damage, B cell depletion in the skin, a moderate reduction in the level of autoantibodies
S. Bosello et al. [200]	Open	9 (SSD)	RTM 1 g once in 2 weeks	Decrease in the skin count, activity index and severity index of the disease (after 6 months). Decrease in IL-6 concentration B cell depletion (n=7)
D. Daoussis et al. [201]	Open	8 (diffuse SSD with ILD)	RTM 375 mg/m^2 4 infusions at a 1 week interval	2 years of follow-up: improvement of lung function (PFT and HRCT) and skin (mRSS and the number of myofibroblasts)
V. Smith et al. [202]	Open	8 (diffuse SSD)	RTM 1 g once in 2 weeks	24 weeks of follow-up: reduced skin sclerosis score, B cell depletion
V. Smith et al. [203]	Open	8 (diffuse SSD)	RTM 1 g once in 2 weeks; repeat course in 6 months	2 years of follow-up: reduction in mRSS, disease activity (DAS), stabilization of internal organ lesions B cell depletion
F.C. Moazedi-Fuers et al. [204]	Open	5 (diffuse SSD with ILD, not responding to CP)	RTM 500 mg twice, then every 3 months for a year	Reduction in mRSS Increase in DLCO and FVC Reduction of pulmonary fibrosis (3 patients) Healing of digital ulcers
D. Giuggioli et al. [210]	Open	10 (SSD)	RTM 375 mg/m^2 4 infusions at a 1 week interval; several cycles	6-72 months of follow-up: reduction in mRSS (6 months), improvement of other skin manifestations (hyperpigmentation, calcification, itching), arthritis ILD: stabilization (n=6), deterioration (n=2) Decrease in concentration of pro-inflammatory cytokines
D. Daoussis et al. [205]	Randomized	14 (SSD)	RTM 375 mg/m^2 4 infusions at a 1 week interval; then in 24 weeks in combination with standard therapy (n=8) Standard therapy (n=6)	In 1 year: improvement in FVC, DLCO and skin lesions
S. Jordan et al. [207]	Case-controlled, registration	88 (SSD)	RTM 1 g once in 2 weeks (n=63) Control (n=25)	Reduction in mRSS (higher in the RTM group) FVC – no change
S.L. Bosello et al. [208]	Open	29 diffused SSD with or without ILD	RTM 1 g once in 2 weeks (if needed – repeated treatment)	70 months of follow-up: mproved skin count, iactivity and severity (in 12 months), FVC and TLC increase, DLCO stabilization, HRCT stabilization (80% of patients)
D. Daoussis et al. [209]	Open Multicentre	51 (SSD with ILD)	RTM 375 mg/m^2 4 infusions at a 1 week interval; (n=33), Standard therapy (n=18)	2 year follow-up on average: FVC increase (in 2 years and for the next 7 years), mRSS improvement (during the entire follow-up period)
M. Thiebaut et al. [210]	Open	39 (SSD)	Various regimens of RTM administration (n=13) Standard therapy (n=26)	Improvement in DLCO (p=0.05), and FVC (p=0.003) vs. the control group
A. Sari et al. [211]	Open Nonconcurrent	14 (SSD and IDL)	Various regimens of RTM administration	15 month follow-up: Increase in FVC (p=0.065), HRST stabilization (n=7), mRSS stabilization
K. Melsens et al. [212]	Open	17 (diffused SSD	RTM 1 g once in 2 weeks	24 weeks of follow-up: improvement in mRSS (p<0.0001), DAS reduction (p<0.0001) stabilization of internal organ damage
M. Boonstra et al. [213]	RCT	16 (early SSD)	RTM 1 g once in 2 weeks (n=8), PL (n=8)	24 weeks of follow-up: Tendency towards improvement in FVC and severity of lung damage In the RTM group: no changes in skin count, B cell depletion
G. Lepri et al. [214]	Open	23 (SSD with IDL)		24 weeks of follow-up: stabilization of lung function
V.S. Vilela et al. [215]	Open	10 (diffused SSD with IDL)	RTM 1 g once in 2 weeks	Improvement of skin manifestations Stabilization of lung function
M. Elhai et al. [216]	Open, cohort	254 (58% with IDL); historical control of 9575 patients	Various regimens of RTM administration	Improvement of skin manifestations, GC dose reduction (or cessation); better outcomes in combination therapy with RTM and MMF;no significant improvement of FVC and DLCO as compared with the control group

Note. PL – placebo, diffused SSD – diffuse form of systemic scleroderma, IDL– interstitial lung disease, mRSS – modified Rodnan skin score, FVC – forced vital capacity, DLCO – diffusion capacity for carbon monoxide, HRST – High-Resolution Computed Tomography, TLC – total lung capacity, PFT – Pulmonary function tests.

In our group of 90 patients with SSD (see Table 3 and 4) with a follow-up period of 12 to 42 months, the leading clinical manifestations were ILD and cardiopathy [217–219]. On RTM therapy the overwhelming number of patients showed an improvement in their general condition (70% had a good response, 24% had an improvement) with a decrease in the severity of shortness of breath and cough, which was accompanied by normalization of the forced vital capacity of lungs and stabilization of the lung diffusion capacity. In the group of patients with SSD in combination with ILD (n=72), a good response to therapy was observed in 52 (73.2%) patients; satisfactory – in 16 (22.6%) patients; and no response was observed in 3 (4.2%) patients. FVC increased from 77.35±19.9 to 82.6±20.7% (p=0.001). The minimum clinically significant increase in FVC = 5% was observed in 41 patients (57.7%). The overall FVC improvement (ΔFVC) reached 5.24%. The safety profile of the therapy was considered good. The most frequent were infectious complications registered in 11 (15%) patients. Of these, 7 developed upper respiratory tract infections, in one case there was a foot phlegmon, in two cases – a urinary infection, and in one – *Herpes zoster*.

Sjögren's Syndrome

SS is the second most common type of IIRD (autoimmune exocrinopathy), the most frequent manifestations of which are dry mouth and eyes, severe discomfort and a wide range of extraglandular (systemic) manifestations (chronic discomfort, arthralgia, lung, kidney, nervous system damage, etc.), developing in 60–80% of patients [220]. Pathological activation of B cells in SS is manifested by hyperproduction of anti-nuclear antibodies (anti-SS-A/Ro and anti-SS-B/La, etc.), IgM RF, hypergamaglobulinemia, less often cryoglobulinemia, an increase in the level of B cells in the peripheral blood that express Bruton tyrosine kinase, and a significant risk of developing B-cell (non-Hodgkin's) lymphoma, primarily MALT (mucosa-associated lymphoid tissue) lymphoma [12].

Data on RTM efficacy in SS treatment are summarized in Table 9. According to a meta-analysis of 4 RCTs (145 patients receiving RTM and 131 patients receiving PL), there were no significant differences in the dynamics of lacrimal gland function in the group of patients receiving RTM (Schirmer test) compared to PL Nevertheless, in the group of patients receiving RTM, there was a significant improvement of clinical manifestations (discomfort) and the salivary glands function [232]. Negative results of controlled studies may be associated with methodological errors, such as incorrect diagnostics, low basal activity level (ESSDAI – EULAR Sjögren Syndrome Disease Activity Index), use of insufficiently validated indices for evaluating the efficacy of therapy, etc. [233, 249]. Our results and data from other authors indicate the efficacy of RTM therapy in patients with high initial disease activity (ESSDAI index) [222–224, 226, 235–237] and in relation to extraglandular (systemic) manifestations of CS (articular, pulmonary, renal, nephrological) [224, 226, 238], including those associated with the development of systemic or cryoglobulinemic vasculitis, and ILD [226, 237, 239]. At the same time, RTM therapy is less effective in the presence of a central nervous system damage resembling multiple sclerosis and in peripheral (non-vascular) neuropathy [240, 241].

The efficacy of RTM therapy is associated with a decrease in IgG concentration [222, 223, 232], IgM RF titres [221, 222, 227, 242]; and the increase of IgM RF concentration on B-cell repopulation is associated with the disease exacerbation [242, 243]. Since high IgM RF titres are risk factors for the development of lymphomas [244], a decrease in IgM RF titres against RTM therapy may have an important clinical significance, since it indicates the potential for preventing malignant lymphoproliferation using anti-B-cell therapy. Although the data on the changes in anti-SS-a/Ro and anti-SS-B/La titres are contradictory [224, 245–247], it is believed that the decrease in the titres of these autoantibodies during RTM therapy may reflect the suppression of the formation of short-lived B cells from CD20+ precursors or direct depletion of short-lived B cells expressing CD20 [247, 248]. RTM therapy is associated with improvement of other immunological biomarkers (decreased concentration of immunoglobulins, β2-microglobulin, and light chains of immunoglobulins) [242, 245], whose hyperproduction in turn correlates with the SS activity (ESSDAI index) [249], as well as the concentration of pro-inflammatory cytokines (IL-6, GM-CSF, TNFα, IL-10), which are potentially expressed by B cell activation [250].

Our data, based on a study of 100 patients with SS, showed RTM was highly effective (see Table 3 and 4). In our patients, glandular manifestations were observed in 60% of cases (16% of them were diagnosed during biopsy with the formation of MALT tissue), systemic extra-vascular manifestations were observed in 40% (including cryoglobulinemia in 32%, monoclonal secretion of immunoglobulins in 26%, skin lesions in 32%, sensory-motor polyneuropathy in 20%, and GN in 16%). The frequency of a good response was 92.5%, and incomplete response was registered in 6.5% of patients. At the same time, the absence of neurological symptoms progression and significant recovery of function were noted in 95%. Among SS patients with GN, a good response was achieved in 97%. The frequency of fatal outcomes did not exceed 2% during the follow-up period of 58 (24–96) months. In all cases, there was no decurrence of cryoglobulinemia as a result of RTM therapy, and monoclonal secretion was no longer detected in 80% of patients on RTM maintenance therapy. It should be noted that the latter effect could not be achieved against the background of standard treatment regimens with GCs, cytostatics and plasmapheresis. Interestingly, the only laboratory parameters that did not respond to RTM therapy were anti-Ro/SS-A, despite a significant decrease in antinuclear factor titres. The relapse rate after discontinuation of RTM therapy was 12%. Among patients with systemic extra-vascular manifestations of SS 34% of patients developed a relapse in 6 months after the first course of RTM, and therefore RTM therapy was continued. In patients with glandular manifestations of SS in all cases, the enlarged large salivary glands were reduced to anatomical boundaries after the first course of RTM. On prolonged RTM therapy, normalization of the ESSDAI damage index and a statistically significant increase in salivation were observed, primarily in cases with preserved residual salivation (>0.5 ml), whereas in the complete absence of secretion before the start of therapy, despite the subject improvement, there was no increase in salivation according to sialometry of the large salivary glands. There was also no statistically significant improvement in lacrimation, despite a decrease in dystrophic changes in the conjunctival and corneal epithelium. None of the patients showed any development of lymphomas.

Idiopathic inflammatory myopathies

IIM is a group of IIRDs of unknown etiology, the main manifestation of which is symmetrical muscle weakness of the proximal parts of the extremities, associated with inflammation of the striated musculature. These include polymyositis (PM);

Table 9 Results of main clinical studies of RTM in SS treatment

Authors	Study design	Number of patients	Treatment regimen	Key findings
S. Dass et al. [221]	RCT	17 (with discomfort of >50 mm VAS)	RTM 1 g once in 2 weeks or PL	In 6 months Discomfort (VAS): >20% reduction on RTM HRQO: SF36 higher in the RTM group
J.M. Meier et al. [222]	RCT (2:1)	30 (SWS >0.15 ml/min)	RTM 1 g once in 2 weeks or PL	48 weeks of follow-up SWS changes: better on RTM B cell changes, RF higher in the RTM group Extraglandular manifestations more intense in the RTM group More discomfort in the RTM group Improvement compared to the baseline on RTM: SWS, B cells, RF, lacrimal glands function, discomfort, SF-36, dryness severity (VAS)
V. Devauchelle-Pensec et al. [223]	RCT (1:1) Multicentre (TEARS)	120 (early): at least 2 of 4 signs (total disease score pain, discomfort dryness) >50 mm VAS	RTM 1 g once in 2 weeks or PL	24 weeks of follow-up: The dynamics of VAS indicators did not differ from PL (TEARS) Improvement of some subjective symptoms was more pronounced in the RTM group
F. Carubbi et al. [224]	Concurrent Multicentre	41 (early active)	RTM or DMARD	120 weeks of follow-up ESSDAI was higher in the RTM group Other clinical parameters (general pain assessment according to the patient, dry syndrome – VAS, SWS, Schirmer test) were more pronounced in the RTM group Reduced infiltration of small salivary glands was more pronounced in the RTM group
S. Jousse-Joulin et al. [225]	RCT Multicentre	28 (early or systemic) at least 2 of 4 signs (total disease score pain, discomfort dryness) >50 mm VAS	RTM 1 g once in 2 weeks or PL	6 weeks of follow-up The structure of salivary glands (ultrasound) is more pronounced in the RTM group The size of the salivary glands and vascularization without changes
J.E. Gottenberg et al. [226]	Registration concurrent observational	78 (Extraglandular or severe glandular manifestations)	Various regimens of RTM administration	6 months to 5 year follow-up: Reduction in ESSDAI Average GC dose tapering
P.M. Meiners et al. [227]	Nonconcurrent	15	RTM 1 g once in 2 weeks Re-treatment (Average interval – 103 weeks)	48 weeks of follow-up Improvement in ESSDAI, B cells, RF, MFI index
D. Cornec et al. [228]	Open	45	Group I (RTM 375 mg/m^2, 4 infusions at a 1 week interval) Group II (RTM 1 g once in 2 weeks vs. PL)	24 weeks of follow-up: SSRI – 50% in both groups Similar B-cell depletion
K. Delli et al.[229]	RCT (2:1)	30 (20 – RTM; 10 – PL)	RTM 1 g once in 2 weeks	According to biopsies (after 24 weeks) RTM therapy led to a decrease in B cells, the number and severity of lymphoepithelial lesions and growth centres
S.J. Bowman et al. [230]	RCT (TRACTISS)	133 (67 – RTM 66 – PL)	RTM 1 g once in 2 weeks	No difference in discomfort and dryness (VAS) as compared with PL
B.A. Fisher et al.[231]	RCT (Phase III) TRACTISS	52 (26 – RTM, 26 – PL)	RTM 1 g once in 2 weeks	Significant improvement of the ultrasound count in the RTM group

Note. HRQL – Health-related quality of life, SWS – chewing-stimulated whole saliva flow, ESSDA – EULAR Sjögren's Syndrome Disease Activity Index, DMARDs – disease-modifying anti-rheumatic drugs

dermatomyositis (DM), juvenile dermatomyositis (JDM); myositis, combined with systemic connective tissue diseases (SCTD) – overlap syndrome; myositis, combined with tumours; myositis with intracellular inclusions, and some other rarer diseases [251]. In 80% of patients with PM/DM, myositis-specific antibodies are detected, primarily antibodies to aminoacetilsinteases of mRNA (anti-Jo-1 and others), whose synthesis is associated with the development of antisynthetase syndrome (ASSD) [252].

Materials of systematic reviews [253, 254] and results of the main clinical studies (Table 10) indicate the efficacy of RTM therapy in IIM treatment. S. Fasano et al. [254] have analysed the results of RTM therapy in 458 patients with refractory IIM course, including 144 patients with PM, 79 patients with ASSD, and 72 patients with JDM. In general, the therapeutic effect was achieved in 78.3% of patients. At the same time, patients in whose sera myositis-specific antibodies (anti-Jo1 and anti-Mi2) were detected, responded better to RTM therapy (and maintained remission >12 months) [265, 268, 271] than patients who tested negative for the antibodies or who had anti-SRP (signal recognition particle), anti-TIF1γ (transcriptional intermediate factor 1γ) and anti-MG (maltase-glucoamylase). At the same time, the relationship between the clinical efficacy of RTM and the changes in anti-synthetase antibody titres was not observed

Table 10 Results of main clinical studies of RTM in IIM treatment

Authors	Study design	Number of patients	Treatment regimen	Key findings
T.D. Levine [255]	Open	6 (DM)	RTM 375 mg/m^2 4 infusions at a 1 week interval	Clinical effect in all patients Increased muscle strength, improved skin lesions, pulmonary function tests (n=2), decreased CPK. A total of 4 patients had a relapse in 29 months
L. Chung et al. [256]	Open	8 (DM)	RTM 1 g once in 2 weeks	Increased muscle strength (MMT index) in 3 patients, no changes in skin lesions (DM Skin Severity index)
M. Sem et al. [257]	Open	11 (ASSD with ILD)	RTM 1 g once in 2 weeks	Short-term improvement of muscle and lung symptoms
R. Valiyli et al. [258]	Open	8 (anti-SRP)	RTM 1 g once in 2 weeks	Short-term improvement of symptoms (n=6)
E.A.M. Mahler et al. [259]	Open	5 (DM), 8 (PM)	RTM 1 g once in 2 weeks	Normalization of CPK and muscle strength; 3 patients achieved clinical remission, 10 patients had a relapse in an average of 7.4 months. The effect was regardless of anti-Jo1 detection
M. Couderc et al. [260]	Open	6 (DM), 12 (MP), 12 (ASSD)	Various regimens	Effect in 16 patients (for15.5 months on average)
I. Marie et al. [261]	Open	7 (ASSD)	RTM 1 g once in 2 weeks	Clinical effect in all patients. HRCT improvement in 5 patients, no progression in 2 patients
C.V. Oddis et al. [262]	Randomized	195 IIM	RTM 375 mg/m^2 4 infusions at a 1 week interval, early or delayed	No effect (no difference between the early and the delayed RTM administration)
R. Aggarwal и соавт. [263]	Randomized	235 IIM	Various regimens	Improvement of skin lesions in DM in children and adults, more often with early RTM administration
L. Unger et al. [264]	Open	13 (PM), 5 (DM), 11 (ILD), 7 (arthritis)	Various regimens	Effect in all 5 patients with DM and 9 patients with PM
H. Anderson et al. [265]	Open	24 (ASSD and ILD)	RTM 1 g once in 2 weeks	Long-term remission; 21% died from infectious complications
L.G. Rider et al. [266]	Randomized	8 (PM), 5 (DM), 5 (JDM)	RTM 1 g once in 2 weeks, early or delayed	8 (44%) patients – DOI after16 weeks, 15 – DOI after 44 weeks
G.J. Keir et al. [267]	Open	10 (IIM+ILD)	RTM 1 g once in 2 weeks	PFT improvement in all patients
Y. Allenbach et al. [268]	Open Phase II	12 (ASSD)	RTM 1 g once in 2 weeks	ncrease in muscle strength (MMT 10) in 7, decrease in CPK, GC dose tapering, ILD improvement (in 5)
S. Barsotti et al. [259]	Open	26 (IIM)	RTM 1 g once in 2 weeks	Reduced CPK (p=0.001), increased muscle strength (MMT8; p<0.001), decreased extra-muscular activity (MYOCAT; p<0.001), reduced skin lesions, arthritis, and improved lung function (in DM), GC dose tapering (p=0.002). Efficacy is higher when anti-Jo1 and anti-SRP are detected
T.J. Doyle et al. [269]	Open nonconcurrent	18 (ASSD)	RTM 1 g once in 2 weeks	HRCT improvement in 88%, FVC improvement in 79% of patients
A.N. Khelkovskaya-Sergeeva [270]	Open	42 (IIM, anti-Jo1 in 18)	RTM 1 g (or 0.5 g) Once in 2 weeks Different number of repeat courses	Reduction of shortness of breath in all patients; FVC improvement (>10%) in 16 patients, DLCO improvement (>10%) in 7 patients, the remaining stabilized. No HRCT progression in 27 patients, improvement in 10, and deterioration in 6 patients

Note. CPK – creatine phosphokinase, MMT – Manual Muscle Testing, MYOCAT – Myositis Cutaneous Assessment Tool, SRP – signal recognition particle, DOI – definitions of improvement.

[255, 272–275]. This indicates that myositis-specific antibodies are synthesized by CD20-negative long-lived plasma cells that are not sensitive to RTM depletion. Altogether RTM therapy was more effective against muscle rather than skin manifestations of IIM, which were reactivated in almost half of the patients after treatment [254]. Heliotropic rash and poikiloderma responded better to RTM therapy [276], and skin rash in paraneoplastic myositis was usually resistant to therapy [277, 278]. Altogether the efficacy of RTM was higher in JDM than in DM in adults [262, 279]. As with other IIRDs, the efficacy of RTM in relation to ILD progression was noted in IIM [265, 269, 272], which corresponds to the data obtained in our study [270].

IgG4-associated disease (IgG4-AD)

IgG4-AD is an immune mediated fibroinflammatory disease that manifests itself in the development of tumour-like foci with characteristic morphological characteristics in various organs and an increase in serum IgG4 levels [280–282]. A char-

acteristic feature of IgG4-AD is a good and rapid response of GC therapy [282–284], which was reflected in the creation of organ-specific diagnostic criteria for this pathology [285, 286]. However, on GC dose tapering (or withdrawal), 30–60% of patients develop a relapse, and long-term use of GC is associated with the development of a wide range of ADRs [287]. This was the basis for the development of new approaches to pharmacotherapy of IgG4-AD, including those related to the suppression of pathological activation of B cells, which play a fundamental role in the immunopathogenesis of the disease [288]. The efficacy of RTM in IgG4-AD (about 90%) was demonstrated in a series of clinical observations [289–301], materials from national registries [302, 303], and open uncontrolled research [304]. The results of RTM administration in IgG4-AD are discussed in detail in our review [284].

Our own experience of RTM administration (usually with repeated courses) in 34 patients with IgG4-AD for a follow-up period of 27 (3–60) months indicates high efficacy of anti-B-cell therapy (see Table 3 and 4). A complete (good) response was observed in 77% of patients, while in the remaining cases there was improvement. All patients had a decrease in serum IgG4 levels, which was less pronounced with incomplete clinical response. In most cases, RTM therapy shows a fairly rapid clinical improvement with the disappearance of paraorbital oedema, reduction of salivary and lacrimal glands to normal anatomical boundaries, and the disappearance of abdominal pain. However, according to visualization methods, the increase in the affected organs persists for a longer time, in some cases there is a pronounced dissociation between the progression of clinical manifestations and the results of imaging.

Prospects for dual anti-B-cell therapy

The discovery of the key role of B cells in the immunopathogenesis of IIRDs served as the basis for the study of B-cell cytokine ligands as possible targets for therapeutic effects. BAFF (B cell-activating factor), also known as BLyS (B lymphocyte stimulator), which is an important component of B cell regulation, function, proliferation, and differentiation, is of particular interest [305]. BAFF belongs to the TNF superfamily and includes two cytokines (ligands), BAFF and APRIL (a proliferation-inducing ligand), which are synthesized by different cells (monocytes, macrophages, DC, etc.) during the immune response. Three types of receptors for BAFF and APRIL – BAFF receptor 3 (BR3), TACI (Transmembrane Activator and Calcium modulator and cyclophylin ligand Interactor), and BCMA (B-cell maturation antigen) – are expressed on the B cell membrane. BAFF interacts more strongly with BR3 than with the other receptors, while APRIL interacts only with TACI and BCMA. There are two forms of BAFF: bound to the cell membrane and soluble (p), with only pBAFF showing biological activity. The interaction of BAFF and BR3 is involved in the regulation of homeostasis of pre-immune B cells, leading to an increase in the survival of autoantibody-producing B cells by preventing their selection and apoptosis. BLM (Benlysta) is fully human mAbs (IgG1λ) that prevent the interaction of pBAFF with cellular receptors of autoreactive transitional and naive B cells, which in turn leads to the suppression of B-cell hyperreactivity, characteristic for SLE (and other IIRDs), manifested, in particular, in the form of hyperproduction of autoantibodies [306, 307].

In recent years, there has been great interest in the possibility of sequential application of RTM followed by the appointment of mAbs to BAFF-BLM, which has been called 'dual anti-B-cell therapy'. It is believed that partially overlapping action mechanisms of RTM and BLM may contribute to an increase in the efficacy of anti-B-cell therapy [308]. There is evidence that the number of B-cell CD20+ and CD20- plasmoblasts is reduced in SLE on BLM therapy, i.e. BLM has a wider spectrum of anti-B-cell activity than RTM [309]. In addition, a high concentration of BAFF in tissues may contribute to B cell resistance to RTM depletion. On BLM therapy, an early repopulation of memory B cells is observed, probably related to their mobilization from peripheral tissues [309]. According to experimental studies, the BAFF recirculation and concentration rate modulates the efficacy of B-cell depletion in tissues, while combined therapy with anti-CD20- and anti-BAFF antibodies leads to more pronounced B cell depletion in the spleen and lymph nodes of mice than with the introduction of only anti-CD20 antibodies [310, 311]. An increase in BAFF concentration should be taken into account a few months after RTM B cell depletion, which may lead to the generation of pathogenic B cell subpopulations secreting autoantibodies. At the same time, an increase in BAFF concentration in the sera of SLE patients treated with RTM is associated with a relapse of the disease [312]. Preliminary results indicate the efficacy of dual anti-B-cell therapy in SLE [313–318]. According to the SYNBIOSE (the Synergetic B cell Immunomodulation in SLE) study (Phase IIa) [318], which involved 16 patients with severe refractory SLE, an improvement in serological indicators, NET (neutrophil extracellular trap formation) expression was observed, correlating with a decrease in disease activity, on combined therapy with RTM (1 g twice) and BLM (10 mg/kg at Week 4, 6, 8, and then every 4 weeks). An early population of B cells (memory B cells and plasma cells) was observed, in the absence of transitional and naive B cells. The predominance of B cells with properties of late stage differentiation suggests that they are formed from B cells of lymphoid tissues, and not from bone marrow progenitor cells. No severe ADRs were observed, but three patients developed hypogammaglobulinemia (IgG<4 g/l), which required the administration of intravenous immunoglobulin. Another Phase II study (CALIBRATE) [319] included 43 patients with LN. After induction therapy with RTM (1,000 mg) in combination with CP and methylprednisolone (100 mg), patients were randomized into two groups: BLM (10 mg/kg according to the standard scheme) in combination with prednisolone or prednisolone monotherapy. An intermediate analysis (after 24 weeks) did not reveal significant differences in the efficacy of therapy (normalization of proteinuria and glomerular filtration rate) in the compared groups (23 and 24%, respectively). Combined B cell depletion did not lead to the development of serious ADRs. Preliminary results indicate the efficacy of RTM and BLM combined therapy [316] and BLM monotherapy [320] in SS treatment. Currently, several studies are planned to research the efficacy of RTM or combined RTM and BLM therapy in IIRD treatment (Table 11).

For the first time, we obtained data on the comparative efficacy of RTM and BLM and double anti-B-cell therapy of RTM and BLM in patients with active SLE (n=54), among which 40 patients received RTM, 7 received BLM, and 7 received double anti-B-cell therapy of RTM and BLM [329, 330]. Combined RTM and BLM therapy resulted in a decrease in disease activity after 3, 6 and 12 months from the start of therapy in all patients. The clinical response correlated with a decrease in the level of anti-dsDNA and an increase in the con-

Table 11 Planned research of RTM therapy in IIRD

Study	Phase	Disease	Treatment regimen	Efficacy evaluation
RECITAL [321]	II/III	Connective tissue diseases in combination with ILD	RTM vs. CP	FVC changes (48 weeks)
BLISS-BELIEVE [322]	III	SLE (n=200)	BLM + RTM + PL vs. BLM + RTM vs. BLM + PL (1:2:1)	Disease control (Clinical SLEDAI-2K <2)
BEAT-LUPUS [323]	II	SLE (n=50)	RTM + BLM RTM + PL	anti-dsDNA changes (52 weeks)
ROOTS [324]	II	SLE (skin, arthritis)	RTM + CP vs. CP	Efficacy and safety of RTM biosimilar
RITUXILUP [325]	III	LN	RTM + CP + MMF vs. CP + MMF	Complete renal response without CP (p.o.)
SYNBIoSe [326]	II	LN (n=16)	BLM + RTM	Reduced concentration of pathogenic antibodies (24 weeks), clinical effect of SLEDAI, LLDAS
RECOVER [327]	II/III	SSD (joint damage) (n=22)	RTM vs. PL	Tender and swollen joint count (26 weeks)
NC02631538 [328]	II	SS	BLM + RTM vs. BLM vs. RTM vs. PL	ADR
EvER-ILD	III	ILD, non-specific interstitial pneumonia (n=122)	RTM + MMF vs. MMF	FVC changes

Примечание. ROOTS – Rituximab Objective Outcome measures Trial in SLE, EvER-ILD – Evaluation of Efficacy and Safety of Rituximab With Mycophenolate Mofetil in Patients With Interstitial Lung Diseases, SLEDAI – Systemic Lupus Erythematosus Disease Activity Index, LLDAS – Lupus Low Disease Activity State.

centration of C3 and C4 components of the complement: in the RTM, and RTM and BLM ($p<0.05$) combination therapy groups after a year of follow-up. On combined RTM and BLM therapy, a decrease in the concentration of IgG ($p<0.02$) and IgM ($p<0.03$) was registered after 12 months, but the overall level of immunoglobulins remained within normal values. Therefore, in patients with active SLE, RTM and BLM monotherapy, as well as double anti-B-cell therapy with RTM and BLM, is highly effective, provides the possibility of managing patients at low/medium supportive doses of GC and helps reduce the risk of developing irreversible organ damage. In another our study, a combination of RTM and BLM was used for the first time in a patient with ANCA-SV characterized by severe granulomatous lung damage despite CP (total 6.2 g) and RTM (2.6 g) therapy [331]. BLM therapy (800 mg twice with an interval of 1 week, then 800 mg per month) was prescribed 12 months after RTM administration and resulted in a significant reduction of foci in the pulmonary parenchyma according to multispiral computed tomography.

This evidences good prospects for RTM and BLM combination therapy in the most severe forms of IIRDs, although its efficacy and especially safety require further study.

Adverse drug reactions

The incidence of infectious complications and other ADRs on RTM therapy was relatively low. Attention should be paid to the frequent development of moderate hypogammaglobulinemia, which, according to retrospective analysis, is registered in more than 50% of patients with various IIRDs [332]. However, a marked decrease in IgG concentration, accompanied by the development of recurrent infections and requiring the administration of intravenous immunoglobulin, is rare (about 5%). Risk factors for hypogammaglobulinemia are low IgG concentration prior to RTM administration, combined CP use, and high cumulative RTM dose [333].

Our data also indicate a relatively satisfactory safety profile of RTM in IIRD treatment, despite the fact that patients had a high risk of infectious complications due to chronic inflammation, organ failure, and a tendency to infection associated with both severe illness and the use of GC and immunosuppressants (see Table 6). Infusion reactions (2–25%), as a rule, which were not severe and did not require the cancellation of RTM, most often developed in patients with CGV and EGPA (20–24%). In SS, infusion reactions (5%) and delayed reactions akin to serum disease (2%) were observed mainly in patients with hypergammaglobulinemia prior to therapy >30%. In the ANCA-negative variant of EGPA, cases of interruption of RTM therapy due to the development of severe bronchospasm have been described. According to our data, in one case, repeated RTM treatment regimen was interrupted due to a severe attack of bronchial asthma. The incidence of serious ADRs in the ANCA-SV group was 27%, including 11% of infectious ARs. In 10% of cases, late delayed neutropenia was observed, usually 6–8 months after the first course of RTM. The highest mortality rate was observed among cases of GPA and MPA with serious ADRs, primarily neutropenia and pneumonia (44 and 50%, respectively). In the SLE group, the frequency of serious infusion-related ARs did not exceed 1%, the majority of serious ARs was infections (10%), and 3% of patients had neutropenia. In groups of other IIRDs, serious infectious ARs were observed less frequently (2–5%) than in SLE or ANCA-SV (10–11%).

Rituximab biosimilars

On the one hand, the introduction of innovative biopharmaceuticals into clinical practice allowed to increase the efficacy of therapy and improve the prognosis in patients suffering from the most severe forms of IIRDs, but, on the other hand, led to a drastic increase in the cost of treatment [334]. Reducing the cost of treatment with expensive biopharmaceuticals and, as a result, increasing the availability of innovative therapies for patients living in countries with limited economic resources, is a priority task for healthcare in all countries of the world. This problem has been partially solved thanks to the development of biosimilars of biopharmaceuticals, whose wide application in clinical practice has become possible due to the expiration of patents for many original biopharmaceuticals [335–339], including RTM [340–343].

In 2001, a biotechnology company BIOCAD was founded in Russia, which is engaged in the production of biosimilars and original biopharmaceuticals. Currently, a number of biopharmaceuticals designed for the treatment of autoimmune diseases, including RTM, are at various stages of development [344]. In 2014, Acellbia® – the first Russian analogue of MabThera® – was registered in Russia. After the completion of a clinical trial in patients with B-cell non-Hodgkin's lymphoma, the data of which confirmed the absence of differences between MabThera® and Acellbia®, several studies of this drug for RA treatment were initiated: BIORA (BIOsimilar of Rituximab in rheumatoid Arthritis) for RA patients [345] and ALTERRA (ALTErnative Rituximab regimen in Rheumatoid Arthritis) [346], both aimed to prove the therapeutic equivalence of the RTM biosimilar (Acellbia®) and the original RTM drug (MabThera®) in RA patients, where prior therapy with DMARDs and TNFα inhibitors was ineffective, and to study the efficacy and safety of Acellbia® (at a dose of 600 mg, twice, at a 2 week interval) as a first-line biopharmaceutical for the treatment of active RA resistant to MT therapy.

The purpose of the BIORA study [345] was to prove the therapeutic equivalence of the RTM biosimilar (Acellbia®) and the original RTM drug (MabThera®) in RA patients where prior therapy with DMARDs and TNFα inhibitors was ineffective. Additionally, the impact of switching from Acellbia® to MabThera® on the main indicators of efficacy, safety and immunogenicity in RA was evaluated. The study was conducted on the basis of 21 accredited medical centres in Russia, Belarus and India. The efficacy of therapy was evaluated in 160 patients, of which 83 patients were included in the group receiving Acellbia® and 77 – in the group receiving MabThera®. The patients in both groups were comparable in age, anthropometric indicators, duration of the disease (on average about 7 years), and disease activity. Throughout the study period, patients received Methotrexate (MT) at a stable dose of 7.5 to 20 mg per week. After 6 months, all patients were evaluated for the efficacy of therapy by the DAS28 index. Starting from Week 24 of participation in the study, if arthritis activity maintained (DAS28 ⩾2.6 points or its increase by 0.6 points or more since the previous examination), the patient was administered a repeated course of RTM therapy. At the same time, a partial crossover was made by re-randomization. If RA relapse developed in the period between Week 25 to Week 47 from the moment of randomization, the patient was also prescribed a repeated course of RTM therapy. Patients who registered RA remission according to DAS28 (=2.6 points) at Week 24 from the initial randomization were followed up for the next 24 weeks. If a relapse developed, the patient was re-randomized and received a second course of RTM therapy followed by a 6-month follow-up. The safety of therapy was characterized by ADR frequency, including serious ones; immunogenicity was characterized by the frequency of occurrence of binding and neutralizing antibodies to RTM (antidrug antibodies – ADAbs) in the serum of patients, identified via solid-phase enzyme immunoassay in a linear range of concentrations of RTM binding antibodies from 7.8 to 250 ng/ml, and via complement-dependent cytotoxicity in the culture of WIL2-S cells (B-lymphoblast line), respectively. The pharmacodynamics of RTM was evaluated by determining the absolute number of CD20- and CD19-positive B cells in the peripheral blood of patients using flow cytometry. The possibility of toxic effects of the studied drugs on other cell types was controlled by the level of CD3-positive cells. It was found that a single RTM infusion caused rapid and pronounced B-cell depletion in the vast majority of patients. The level of CD3-positive cells did not significantly change.

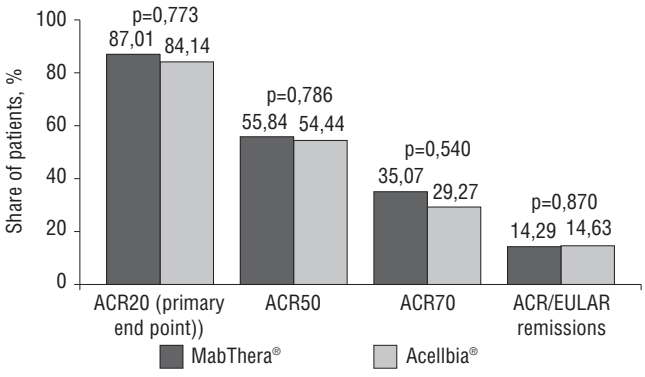

Fig.1 Comparative efficacy of Acellbia® and MabThera® after 24 weeks

In 24 weeks after the start of treatment, improvement in ACR20 was observed in the Acellbia® group in 84.1% (95% PCS 74.75–90.50) of patients, and in 87% of patients in the MabThera® group (95% PCS 77.71–92.79%; p=0.773; Fig. 1). There were no difference in the efficacy of treatment according to the ACR50 and ACR70 criteria. The ACR50 effect was registered in 55.8% of patients in the MabThera® group and in 54.4% of patients in the Acellbia® group (p=0.786), and according to ACR70 – in 35.1% and 29.3% of cases, respectively (p=0.540). Improvement corresponding to the remission criteria (ACR/EULAR) was observed in 14% of patients in both groups.

As already noted, the main task of the second stage of the study was to research the impact of switching patients previously treated with MabThera® to Acellbia® and vice versa, on the efficacy, safety and immunogenicity of the therapy. The study group included 106 patients, 52 of whom received Acellbia® and 54 patients, who received MabThera®. The following groups of patients were identified:

- *MM Group*. Patients who received MabThera® in the first and second stages of the study (n=26).
- *MA Group*. Patients who received MabThera® at the first stage and Acellbia® at the second stage of the study (n=27).
- *AA Group*. Patients who received Acellbia® in the first and second stages of the study (n=25).
- *AM Group*. Patients who received Acellbia® at the first stage and MabThera® at the second stage of the study (n=28).

Each endpoint was compared in groups: MM Group vs. AA Group, MM Group vs. MA Group, AA Group vs. AM Group. In 24 weeks after the repeated course of RTM therapy (i.e., at Week 48 of the study), more than a third of patients in all groups had an ACR70 effect: 34.6% in MM Group; 40% in AA Group (p=0.914); 34.6% in MM Group and 40.7% in MA Group (p=0.779); and in AA Group and AM Group – 40% and 39.3%, respectively (p=0.819). A comparable frequency of the ACR50 effect was achieved in all groups: 61.5% and 52% in MM and AA Groups (p=0.686); 61.5% and 51.9% in MM and MA Groups (p=0.664); 52% and 64.3% in AA Group and AM Group (p=0.229). The ACR20/50/70 effect did not differ in the compared groups until the end of the study (p>0.05; Fig. 2). These preliminary results indicate the potential interchangeability of the original MabThera® drug and its biosimilar Acellbia®.

Both drugs demonstrated favourable safety and tolerability profiles and did not differ in the frequency and spectrum of ADRs. In general, ADRs were reported in 54 (59.3%) patients in the Acellbia® drug group and in 46 (54.1%) patients in the MabThera® drug group. No fatalities were recorded during the entire observation period. The ADR spectrum corresponded to the literature data concerning the safety of the original RTM drug (MabThera®). ADAbs were rarely detected, and their synthesis did not affect the efficacy of therapy and the development of ADRs.

In general, the results obtained indicate a favourable experience of using Acellbia® in RA patients; there are no differences in pharmacokinetics, pharmacodynamics, efficacy, safety or immutability as compared with MabThera®, which indicates the possibility of its use in RA treatment.

In recent years, data have been obtained on the possibility of using RTM at lower doses [347] than in standard recommendations (and instructions) on the administration of this drug [348]. This was the basis for the ALTERRA study [346], which aimed to study the efficacy and safety of using Acellbia® (at a dose of 600 mg, twice, at a 2 week interval) as the first-line biopharmaceutical for the treatment of active RA resistant to MT therapy. ALTERRA RTC was conducted on the basis of 23 accredited medical centres. The study included 159 patients aged 18 to 80 years with active RA. Entry criteria: written informed consent; the patient was diagnosed with RA at least 6 months before the study; the presence of RA activity at the time of screening (⩾8 swollen and ⩾8 painful joints, the level of C-reactive protein (CRP) in serum ⩾7 m/l and/or ESR ⩾28 mm/h; seropositivity for RF and/or antibodies to cyclic citrullinated peptide (anti-CCP): anti-CCP ⩾20 U/ml and/or RF-IgM level above the upper limit of normal); documented regular MT intake for 12 weeks, including the last 4 weeks before the study, at a stable dose of 10 to 25 mg/week. After stratification by age (<40 years / ⩾40 years), seropositivity for anti-CCP, and activity of arthritis according to the DAS28-ESR index (3.2–⩾5.1), patients were randomly assigned at a 2:1 ratio to one of the two groups: Acellbia® + MT group (Group 1) and PL + MT group (Group 2).

In both groups, patients received MT at an average dose of 15 mg/week; in the main group, patients received the drug Acellbia® at a dose of 600 mg on Day 1 and Day 15; in the control group – PL infusion on Day 1 and Day 15. If during the follow-up examination, starting from Week 15, a patient did not show a 20% improvement in the number of swollen and painful joints (compared to the screening), a new DMARD was prescribed to increase the efficacy of therapy in this category of patients. If RA activity was detected [DAS28-4 (ESR) ⩾2.6 at the follow-up examination after 24 weeks or later, the patient was given the first or repeated course of Acellbia®. The duration of the follow-up was 52 weeks. The main end point in the study for evaluating the efficacy was the number of patients who achieved a 20% improvement in ACR criteria at Week 24 of follow-up; the secondary end points were the number of patients who achieved a response according to the ACR20/50/70 and ACR50/70 criteria at Week 16 and Week 24, respectively, the change in the average DAS28-4 (ESR) index, and the changes of the HAQ-DI and SF36 indices. The demographics and RA characteristics were comparable in patients in the Acellbia® + MT and PL + MT groups.

At Week 24 of the study, the number of patients who reached ACR20 was 65.7% in the Acellbia® + MT group, and 29.4% in the PL + MT group (p<0.0001). In addition, there were significant differences at Week 24 between the groups in the frequency of ACR50 achievement: 28.4% in the study drug group and 5.9% in the comparison group (p=0.001). In the Acellbia® + MT group, the ACR70 effect occurred in 12.8% of patients and only in 2.0% of patients in the PL + MT group (p=0.036; Fig. 3). When evaluating the average change in the HAQ-DI index, a significantly more pronounced decrease was also shown in the Acellbia® + MT group (p=0.008). The quality of life analysis (SF-36 survey) showed the same improvement in the physical and psychological quality of life; both groups were characterized by a sufficient increase in the physical and psychological score during the study period, but in the Acellbia® + MT group, the quality of life indicators significantly exceeded those in the PL + MT group, which indicates a more pronounced significant improvement in the quality of life in patients of the RTM group for both physical and psychological component.

Therefore, it was found that the use of Acellbia® at a dose of 600 mg in combination with MT is significantly superior over the use of MT and PL in patients with active RA who have not previously received biopharmaceutical therapy.

At least one ADR/serious ADR (SADR) was registered in 48 (44.9%) patients in the Acellbia® + MT group and in 22 (43.1%) patients in the PL + MT group (p=0.974). During the entire study period, none of the participants had therapy cancelled due to ADR/SADR, and there were no fatal outcomes. Among ADRs, lymphopenia (in 9.4% of patients in the main group and in 7.8% of patients in the control group; p>0.005), upper respiratory tract infections (acute respiratory infections, acute nasopharyngitis, acute pharyngitis, acute bronchitis) were the most frequently registered. Cardiovascular system disorders, hematological toxicity (anemia, leukopenia, neutropenia), as well as infusion reactions were registered less frequently. After lymphopenia, anemia was the second most common type of ADR in the blood system. It was registered in 3.7% and

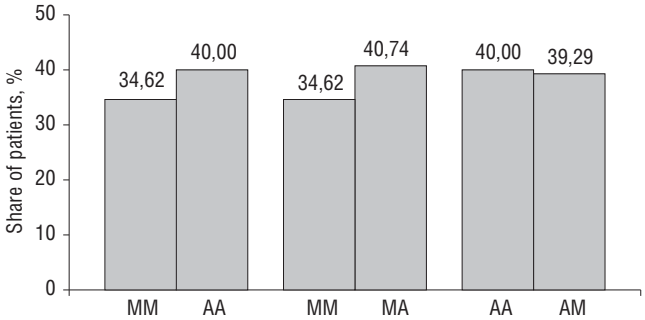

Fig. 2. Efficacy of therapy when switching from Acellbia® to MabThera® and vice versa after 48 weeks

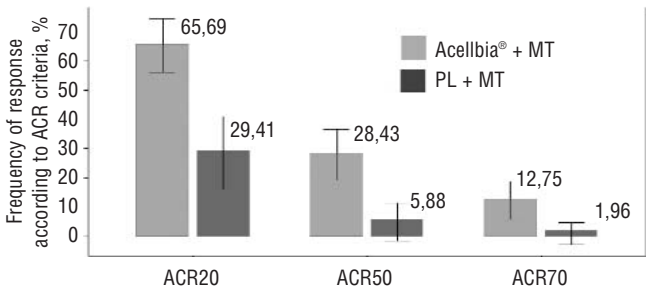

Fig. 3. Efficacy of therapy in the main and control groups

11.8% of patients in the main and control groups, respectively (p=0.078). Neutropenia was registered in 4.7% and 2% of patients, respectively (p=0.665), leukopenia – in 4.7% of patients in the main group and was absent in the control group. Other ADRs occurred very rarely. In general, when comparing the two groups, there were no statistically significant differences for all grade 3–4 ADRs. SADRs were reported in 5 patients: in 3 (2.8%) patients in the main group and in 2 (3.9%) patients in the control group. Right-sided lower-lobe pneumonia, hypertensive crisis, and orchiepididimitis were registered in the Acellbia® + MT group. Two SADRs were registered in the PL + MT group: gastroenteritis and acute hepatitis of unspecified origin with minimal activity. Infusion reactions occurred in only four patients (3.7%) in the Acellbia® + MT group, three infusion reactions had the 2nd degree of severity and one reaction had the 3rd degree of severity. All of them, according to the researchers, were associated with the therapy. ADAbs formation was observed in 21.7% and 4.1% of patients in the Acellbia® + MT and PL + MT group, respectively (p=0.006).

The analysis of safety data (the frequency of all registered ADRs) indicates that there are no significant differences between patients in the main and control groups and corresponds to the safety data of MabThera®; no unusual ADRs were registered. It was noted that the presence of RTM antibodies with binding and neutralizing activity did not affect the efficacy and safety of therapy.

The results of the ALTERRA study indicate that Acellbia® therapy at a dose of 600 mg (two infusions at a 2 week interval) in combination with MT in RA patients who have not previously received biopharmaceuticals is more effective in suppressing the clinical and laboratory activity of RA [ACR20/50/70, DAS28 – 4(ESR), CRP, ESR] and improving the quality of life of patients (HAQ-DI and SF-36) than MT monotherapy. The use of a lower dose of Acellbia® is justified by data concerning the comparison of the clinical efficacy of RTM (MabThera®) at low and standard doses. The results of large-scale RCTs indicate a similar efficacy of two RTM infusions at a dose of 500 mg and at a dose of 1,000 mg [349–359] (Table 12). Most of the patients included in these studies were seropositive for RF, had developed RA, and were resistant to DMARDs. A small number of patients included in the DANCER and MIRROR studies were resistant to TNFα inhibitors, while the SERENA and RA-SCORE studies included patients with insufficient effect of only DMARDs, and the IMAGE study included patients with early RA who had not previously received MT or other DMARDs. In all studies, RTM treatment was performed in combination with MT. According to a meta-analysis of these RCTs [347], there were no significant differences in efficacy between groups of patients receiving RTM at low (500 mg 2 infusions) and standard (1,000 mg 2 infusions) doses after 24 and 48 weeks. There was an unreliable trend towards higher efficacy of standard RTM doses (ACR70, after 24 weeks) and ACR50 and DAS28 after 48 weeks. According to the 'non-inferiority' criterion (the efficacy/safety/tolerability of the treatment method is not lower than that of active control), low doses of RTM are not inferior to high doses in terms of ACR20, ACR50 and DAS28 changes after 24 and 48 weeks. The long-term results of the IMAGE study, according to which similar efficacy and safety of low and high doses of RTM were maintained for 104 weeks [354], are of interest. According to x-ray tests, there were no significant differences in suppressing the progression of joint destruction between different RTM doses. A more pronounced progression of joint destruction (modified Sharp/van der Heijde index) within 0.35 units in patients receiving low doses of RTM has no clinical significance in patients with early RA, since clinically significant differences in this index are 5 units per year [360, 361]. According to the RA-SCORE study [359], which researched the parameters of magnetic resonance imaging (MRI) after 52 weeks of treatment with high and low doses of RTM, there were no significant differences in the suppres-

Table 12 Efficacy of different RTM doses in RA according to RCT data

RCT	Efficacy				
	ACR20, %	ACR50, %	ACR70, %	EULAR criteria good/moderate response, %	DAS28 < 2,6 (remission), %
DANCER [349], 24 weeks of follow-up					
RTM 500 mg twice + MT	55*	33*	13*	73*	n/a
RTM 1000 mg twice + MT	54*	34*	20*	67	n/a
PL + MT	28	13	5	37	n/a
MIRROR [358], 48 weeks of follow-up (2 courses)					
RTM 500 mg twice + MT	64**	39	20	73	9
RTM 500 mg twice + MT, 1000 mg twice + MT	64	39	19	72	13
RTM 1000 mg twice + MT	72***	48	23	89	19
IMAGE [364], 52 weeks of follow-up (2 courses)					
RTM 500 mg twice + MT	77*	59*	42*	39*	25*
RTM 1000 mg twice + MT	80*	65*	47*	42*	31*
PL + MT	64	42	25	18	13
SERENE [352], 24 weeks of follow-up					
RTM 500 mg twice + MT	54.5*	26.3*	9.0*	66.5*	9.6*
RTM 1000 mg twice + MT	50.6*	25.9*	10.0*	63*	9.4*
PL + MT	23.3	9.3	5.2	33.8	2.3

Note. * – p=0.0001–0.05, when comparing RTM + MT with PL + MT; ** – p=0.815 (RTM 500 mg twice, 2 courses, as compared to RTM 500 mg twice and 1 g twice); *** – p=0.2 (RTM 500 mg twice, 2 courses as compared to RTM 1 g twice, 2 courses); n/a – no data.

sion of MRI signs of synovitis, osteitis, erosions and narrowing of the joint gap. Interestingly, the improvement of the DAS28-ESR, DAS28-CRP, and HAQ index (after 24 and 54 weeks) as compared with PL were marked only in patients receiving low doses of RTM. The SMART open study [362] included patients with RA who were resistant to TNFα inhibitors (n=152); the efficacy of the second course of RTM (RTM infusion at doses of 1,000 and 500 mg) was compared in them, after achieving a moderate/good response to therapy according to the EULAR criteria (6 months) after the first course of RTM at a standard dose. The endpoints of this study were area under the curve (AUC) of the DAS28-SRB index (after 104 weeks), the need for repeated RTM courses to maintain remission, and the duration of the effect. It was found that the efficacy of RTM at a dose of 500 mg as compared with 1,000 mg meets the non-inferiority criterion, and the need for repeated courses of therapy was similar. Analysis of the results of cohort studies [363–365] also shows similar efficacy of high and low doses of RTM (good effect according to the EULAR criterion, changes of the DAS28 index). It should be emphasized that more complete depletion of B cells, correlating with RTM efficacy, occurs more often on treatment with high rather than low doses of RTM [364]. Therefore, approaches to choosing the optimal RTM dose for RA require further study to address the problem of personalized therapy of this disease [366]. At the same time, it is necessary to take into account dose-dependent ADRs during RTM treatment, such as late neutropenia [367] and hypogammaglobulinemia [368]. It is also necessary to take into account the successful results of low-dose RTM in other autoimmune diseases, such as bullous pemphigoid [369, 370], membranous nephritis [371], idiopathic autoimmune hemolytic anemia [372] and primary immune thrombocytopenia [373], resistant thrombocytopenia in SLE [374].

The safety profile of combined therapy with Acellbia® and MT corresponds to the data obtained when studying MabThera® in combination with MT. The most frequent ADR during Acellbia® therapy (as well as with MabThera®) were infusion reactions, which were registered significantly more frequently (in about a third of patients) during the first rather than the second and subsequent courses of therapy. The immunogenicity of Acellbia® did not differ from the immunogenicity of MabThera® and did not depend on the dose of the drug [375]. It is also believed that the synthesis of anti-chimeric antibodies to RTM does not affect efficacy, including in repeated courses of therapy, and the risk of infusion reactions [375–377].

It can be assumed that the wider use of Acellbia® in low doses, including as the first-line biopharmaceutical with insufficient efficacy of MT monotherapy, will improve the prognosis in severe RA patients, resistant to standard therapy, and make it more accessible due to the lower cost of treatment with this drug.

This position is confirmed by the preliminary data we obtained concerning the use of MabThera® and Acellbia® in real clinical practice [378] according to the register of RA patients – 'OREL' [379].

The analysis included 349 patients who were started on RTM therapy (as of October 2018). All patients received RTM therapy: 340 patients received original drug (MabThera®) and 9 received its biosimilar (Acellbia®), with 263 patients (75.4%) taking it in combination with DMARDS and 86 (24.6%) patients receiving monotherapy. MT was the most commonly used DMARD, with 172 patients (65.4%) receiving it; Leflunomide was prescribed to 72 (27.4%) patients; Sulfasalazine was administered to 2 patients (0.8%); Hydroxychloroquine – to 11 patients (4.2%), Azathioprine – to 3 patients (1.1%), and Cyclosporine – to 3 patients (1.1%).

Out of the 349 patients included in the study, RTM was the first prescribed biopharmaceutical for 272 (77.9%) patients (263 patients received the original drug and 9 received the biosimilar), and 77 (22.1%) patients had already been taking a biologic medical product. Most commonly RTM was administered when Infliximab (INF) was ineffective/poorly tolerated, that is in 37 patients (48.1%) (including two patients who were started on the RTM biosimilar therapy); in 16 patients (20.8%) Adalimumab (ADA) had no effect; in 6 patients (7.8%) – Etanercept (ETC); in 12 patients (15.6%) – Abatacept (ABC) and in 6 patients (7.8%) – Tocilizumab (TCZ). The majority of patients – 205 (58.7%) – received three courses of RTM therapy or more, one course of RTM was given to 109 patients (31.2%), and two courses were given to 35 (10%) patients. The maximum number of therapy courses was 12.

The use of RTM was accompanied by a significant decrease in the activity of the disease after the first course of therapy. After the first course, remission / low disease activity was noted in 23% of patients, reasonable activity – in 59.6%, high activity maintained in 17.5% of patients; after the second course of therapy, remission / low disease activity was achieved in 26.2% of patients, after the third – in 39.6%, after the fourth – in 36.9% of patients (Fig. 4). A decrease in the level of acute phase indicators (CRP and ESR) was noted: after the fifth course of therapy, the concentration of CRP decreased by 1.4 times and amounted to 7 [1.2; 17.9] mg/l, while ESR decreased by 1.8 times and amounted to 10 [5; 20] mm/h ($p<0.05$). On therapy, a sufficient decrease in the level of IgM RF was detected; after the third course of RTM, its concentration was 10.6 [9.5; 27.7] MU/ml, and after the fifth course, its content decreased fivefold and amounted to 9.5 [9.5; 52.2] MU/ml. All patients were divided into two groups depending on their previous treatment with biopharmaceuticals: the first group consisted of patients without prior experience of taking biopharmaceuticals (n=272), and the second group consisted of patients who received previous biologic therapy (n=77). We did not find a significant difference in the efficacy of RTM therapy in the two groups of patients, depending on the previous treatment with biopharmaceuticals. Fifteen patients were switched from the original drug (MabThera®) to the biosimilar (Acellbia®). Before

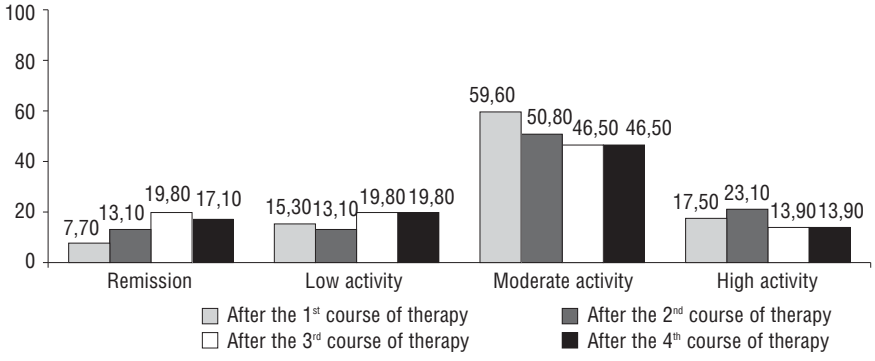

Fig. 4. RA activity on RTM therapy, %

switching, the patients received an average of 4 courses of RTM therapy. Three months before the switching of therapy, the patients achieved moderate disease activity (DAS28–3.5 [3.02; 3.67]); 3 months after switching, the DAS28 value was 3.37 [3.09; 3.8], there was no significant difference in disease activity 3 months before and 3 months after the switching of therapy ($p>0.05$; Fig. 5).

Therefore, the switching of patients from the original drug (MabThera®) to the biosimilar (Acellbia®) did not lead to a relapse of the disease neither it caused any significant changes in the activity of the disease. The use of the original RTM and its biosimilar led to a significant decrease in the activity of the disease, the level of acute phase indicators and the content of autoantibodies in the blood serum. This corresponds to the results of a meta-analysis involving 1,747 patients from six randomized controlled trials, indicating that improvement by ACR20 criteria was significantly more frequently registered in the biosimilar group (OR 4.30; 95% PCS 1.75–10.91) and the original drug (OR 4.07; 95% 2.51–7.18), as compared with the PL group [380]. There were no significant differences in the efficacy (ACR20/50/70 criteria) and safety of therapy between the original drug and the biosimilar groups. H. P. Tony et al. [381] obtained similar results when evaluating the efficacy and safety of switching patients with RA from the original RTM to its biosimilar (GP2013). The analysis included 107 patients with RA who had previously received RTM therapy in combination with MT of any duration. If repeated infusions of the drug were necessary, patients were randomized into two groups: patients in the first group were started on the biosimilar (GP2013), while those in the second continued taking the original drug. In the two treatment groups, there was a comparable frequency of infusion reactions (11.3% and 18.5%), the formation of neutralizing antibodies was not registered, and there were no clinically significant differences in the frequency of ADRs between the groups.

Studying the changes in the cytokine profile is important for monitoring and predicting the efficacy of biopharmaceutical therapy [35, 382–384]. We studied the dynamics of autoantibodies and cytokines concentration in RA patients after 12 and 24 weeks on Acellbia® therapy in comparison with MabThera® in 54 patients with RA. Clinical and laboratory parameters were analysed immediately before the start of therapy, after Week 16 and Week 24. ESR was determined using the standard international Westergren method (normal range ⩽30 mm/h); serum concentrations of CRP and IgM RF were measured using an immuno-nephelometric method on a BN ProSpec (Siemens, Germany) analyser, and a highly sensitive latex-enhanced test was used to determine CRP (sensitivity of 0.175 mg/l). The normal level of CRP in the blood serum was ⩽5.0 mg/l, the IgM RF upper limit of the normal was taken as a concentration equal to 15.0 MU/ml. Assay of anti-CCP in blood serum was performed by enzyme immunoassay (ELISA) using commercial reagent kits (Axis-Shield, UK, upper limit of the norm 5.0 U/ml). Concentration of 27 cytokines in blood serum (IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF-basic, G-CSF, GM-CSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGF bb, RANTES, TNFα, VEGF) was identified via multiplex xMAP technology using Bio-Plex array system analyser (BIO-RAD, USA). Before the RTM therapy, DAS28 (5.9 [5.4; 6.8]), SDAI (33.1 [23.8; 44.6]), and CDAI (29.6 [22.2; 38.3]) indices corresponded to high RA activity. By Week 24 of RTM therapy, good/moderate response according to EULAR criteria was registered in 33 (97%) patients in the first group and in 17 (85%) patients in the second group; remission according to DAS28 (<2.6) was achieved in 8 (23.5%) and 4 (20%) patients; according to SDAI (⩽3.3) – in 5 (14.7%) and 2 (10%) patients; and according to CDAI (⩽2.8) – in 6 (17.6%) and 1 (5%) patients, respectively.

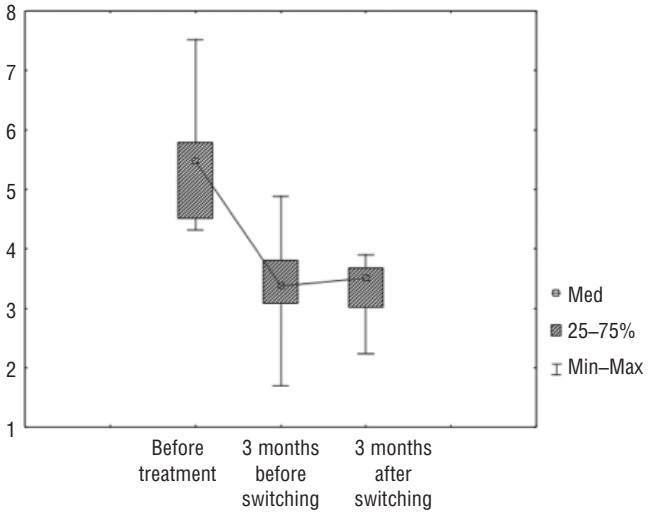

Fig. 5. Changes in the DAS28 index in the group of patients switched from original MabThera® to its biosimilar Acellbia®

In the MabThera® group (Group 1) the levels of IL-1RA, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, eotaxin fibroblast growth factor (FGF-basic), GM-CSF, IFNγ, IFNγ-inducible protein (IP-10), monocytic chemoattractant protein 1 (MCP1), macrophage inflammation protein 1α (MIP1α), MIP1β, platelet-derived growth factor (PDGF) bb, and vasculoendothelial growth factor (VEGF) prior to the therapy were significantly higher by more than 30% as compared with the control group, while the concentration of IL-1β and granulocyte colony-stimulating factor (G-CSF) was lower than in the control group ($p<0.05$), and the content of IL-5, IL-17 and TNFα did not significantly differ from that of donors ($p>0.05$) Among patients who received Acellbia® (Group 2), there was a significantly higher concentration of pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-12, IL-15, TNFα), chemokines (IL-8, MIP1β, MCP1) and growth factors (G-CSF, FGF) compared to healthy donors ($p<0.05$); the level of a number of anti-inflammatory cytokines was higher among RA patients (IL-4, IL-5, IL-9, IL-10, IL-1RA, eotaxin; $p<0.05$); the content of individual growth factors (IL-7, VEGF), chemokines (MIP1α, IP10) and pro-inflammatory cytokines (IL-13) was either lower or did not differ from the control group. By Week 24 of treatment, in the MabThera® group as a whole there was a significant reduction in the levels of pro-inflammatory (IL-1I, IL-2, IL-6, IL-12, IL-15, IFNγ, TNFα), anti-inflammatory (IL-1RA, IL-5, IL-9, IL-10, IL-13) cytokines, growth factors (IL-7, GM-CSF, FGF-basic) and chemokines (MSR1) by more than 30% ; changes in the concentration of IL-8, Eotaxin, G-CSF, MIP1β, PDGF-bb, and VEGF were not statistically reliable ($p>0.05$), and the concentration of MIP1β varied by less than 30% relative to the baseline level. Among patients with a good response to therapy by Week 24 of RTM use, there was a significant decrease by more than 30% in the levels of IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12, IL-13, IL-15, G-CSF, GM-CSF, IFNγ, IP10, MCP1, MIP1α, TNFα, and VEGF; there was no relevant change in the levels of IL-10, IL-17, eotaxin, MIP1β, PDGF-bb ($p>0.05$). By

Week 24, in the group of patients with a satisfactory response to therapy or no response, there was a significant decrease in IL-1RA, IL-2, IL-6, FGF-basic, and GM-CSF, there was no statistically reliable change in the levels of other indicators ($p>0.05$). The use of Acellbia® was also accompanied by a rapid and pronounced decrease in the concentration of almost the entire spectrum of cytokines 12–24 weeks after the first infusion. In general, after 12 weeks the group showed a decrease in the level of pro-inflammatory (IL-1β, IL-2, IL-6, IL-12, IL-15, IL-17, IFNγ) and anti-inflammatory (IL-4, IL-5, IL-9, IL-10, IL-13, IL-1RA, Eotaxin) cytokines, growth factors (IL-7, G-CSF, GM-CSF, VEGF) and chemokines (IL-8, MIP1α, MIP1β, MCP1; $p<0.05$). After 24 weeks, there was also a decrease in the concentration of IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, G-CSF, IFNγ, IP10, MCP1, MIP1β, TNFα, and VEGF ($p<0.05$); the content of MIP1α varied by less than 30% as compared with the baseline, there was also an increase in the level of GM-CSF and RANTES ($p<0.05$). In patients with a good response to therapy, in contrast to patients with a moderate effect of the drug, there was a significant decrease in IL-4, G-CSF, and MIP1α levels after 12 and 24 weeks of treatment, as well as an increase in the level of RANTES after 12 weeks of treatment ($p<0.05$). In the group of patients with a moderate response to therapy, on the contrary, there was a significant decrease in the VEGF content. Prior to therapy, there was a positive correlation between IL-1β, IL-6, and VEGF levels and clinical and laboratory indicators of disease activity. After 24 weeks, a negative correlation between the disease activity indicators and the level of anti-inflammatory cytokines (IL-4, IL-13 and eotaxin) was detected, as well as a positive correlation with the levels of IL-6 and IL-8. To identify early predictors of response to therapy, we analysed the levels of profile cytokines in groups of patients depending on the response according to the EULAR criteria, as well as those who achieved remission according to DAS28, SDAI and CDAI indices by Week 24 of therapy. As possible early predictors of response by Week 24 we can distinguish an increase in the level (pg/ml) of IL-17, both initial, which was registered among patients of the first group (107.2 [25.5; 433.3] and 17.3 [6.1; 120.5]), and after 12 weeks of treatment: among patients with good and moderate/no response to therapy, respectively ($p<0.05$). When comparing basal cytokine levels in groups with different clinical responses at Week 24, patients with a good response to therapy showed increased concentrations of IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-8, IL-9, IL-10, IL-12, IL-15, IL-17, IFNγ, MCP1, MIP1α, TNFα, and VEGF.

Therefore, when studying the changes in cytokine levels on therapy with the original RTM (MabThera®) and its biosimilar (Acellbia®), a similar effect of the drugs on the level of cytokines, chemokines and growth factors was noted. Both drugs lead to a decrease in the concentration of pro-inflammatory cytokines: IL-1β, IL-2, IL-6, IL-12, IL-15, IFNγ, TNFα; anti-inflammatory cytokines: IL-1RA, IL-5, IL-9, IL-10, IL-13; growth factors: IL-7, GM-CSF, FGF-basic; and chemokines: MCP1 in 12–16 weeks after the first infusion.

In other studies, the changes in indicators of the acute phase of inflammation (ESR, CRP), autoantibodies (IgM/IgA RF, anti-CCP), G, M and A-class immunoglobulins, and the number of B-lymphocytes were studied in RA patients after 12 and 24 weeks on Acellbia® therapy [385, 386]. Among the patients included in the study, 18 (90%) were positive for IgM RF, 16 (80%) – for IGA RF, 20 (100%) – for anti-CCP, and 18 (90%) – for antibodies to modified citrullinated vimentin (AMCV). High-positive levels of IgM RF were registered in 17 (85%) patients, IgA RF – in 10 (50%) patients, anti-CCP – in 16 (80%) patients and AMCV – in 17 (85%) patients. Prior to RTM therapy, the level of AMCV was significantly higher in the group of patients with a good response of therapy than among those with a satisfactory response or no response at all (MU 1000 [1000; 1000] and 225.9 [60.8; 654.5] U/ml, respectively; $p<0.05$). There was also a tendency to a higher level of IgM RF among patients with a good response to RTM (414 [263; 502] and 170 [52.5; 519] MU/ml; $p=0.05$), while the levels of other indicators in these groups of patients did not differ significantly. On Acellbia®, a significant decrease in the concentration of IgM RF in the sera of those who responded to therapy was detected at Week 12 and 24 and was 79.7% and 87.1% of the initial level, respectively (Table 13). At the same time, 10% of IgM RF-positive RA patients had seroconversion in IgM RF-negative results. The level of IgA RF significantly declined by 72% and 85% from the baseline, respectively, at Week 12 and 24 in patients with a good response, and in patients with a satisfactory response – by 59.7% at Week 12 and by 67.5% at Week 24. For the group as a whole, the average value of the IgA RF content corresponded to the norm by Week 24. The concentration of anti-CCP in sera remained high throughout the follow-up. However, 15% of anti-CCP-positive patients had a seroconversion of anti-CCP. The level of AMCV significantly decreased – by 46.4% and 60.8%, respectively – in 12 and 24 weeks after the start of RTM therapy. CD19+ B-lymphocyte depletion was achieved by Week 12 in all patients (absolute content – 0), by Week 24 there was an increase in the level of CD19+ B-lymphocytes (0.0030 [0.0003; 0.0270] • 10^9/l), by Week 24 depletion remained in 14 (70%) patients, and two patients who did not respond to the therapy registered almost complete recovery of B-lymphocyte levels by Week 24. A significant decrease in the IgG levels among RTM responders was observed by Week 24 and amounted to 15.4% of the baseline level. A decrease in IgM levels was observed in 36.4% of patients in 24 weeks. A significant decrease in the IgA level by 37.3% was also registered during Week 24. However, the average levels of immunoglobulins in all groups of patients remained within the normal range.

The results show that the use of RTM biosimilar (Acellbia®) in patients with active RA, resistant to standard treatment with DMARDs and GCs, leads to a significant decrease in the activity of the disease, laboratory indicators of inflammatory activity (ESR, CRP), as well as the concentration of auto-antibodies (IgM/IgA RF, AMCV). According to the lit-

Table 13 Dynamics of disease activity, levels of acute phase indicators and autoantibodies on RTM therapy [25th; 75th percentiles]

Indicator	DAS28	ESR, mm/h	CRP, mg/l	IgM RF, MU/ml
Baseline	4.7 [3.8; 5.6]	18 [10; 37]	10 [3.2; 35.2]	50 [13.4; 189]
After the 1st course	4.3 [3.6; 5.1]*	12 [6; 25]*	6.7 [2; 18.8]*	23.5 [9.5; 102.8]*
After the 2nd course	4.1 [3.3; 5.01]*	12 [6; 22]*	5.8 [1.8; 15.1]*	18.6 [9.5; 82]*
After the 3rd course	3.9 [3.2; 4.7]*	10 [5; 21]*	7 [1.9; 13.9]*	10.6 [9.5; 27.7]*
After the 4th course	4.15 [3.5; 4.5]*	10 [7; 18]*	7 [1.9; 20.7]*	11.6 [9.5; 23]*
After the 5th course	3.6 [3.4; 4.3]*	10 [5; 20]*	7 [1.2; 17.9]	9.5 [9.5; 52.2]

Note. *$p<0.05$ as compared with the baseline

erature, RTM causes a significant decrease in the level of CRP and ESR, reaching 40% 28 weeks after administration of the drug [387–389]. In our group of patients, the normalization of CRP concentration was observed by Week 24, and ESR normalized as early as 12 weeks after the first infusion of the drug. Along with a decrease in the levels of markers of the acute phase of inflammation (ESR, CRP), there was a significant decrease in the concentration of IgM/IgA RF and AMCV in the absence of significant changes in anti-CCP. Other authors have also registered a 55–73% decrease in the concentration of IgM RF after 8 weeks of RTM therapy [390–392]. Literature data on the effects of RTM on the level of IgA RF in the sera of RA patients are contradictory. A study of A. Tsiakalos et al. [393] demonstrated a significant decrease in IgA RF level 1–2 months after RTM administration, but M. Bokarewa et al. [394] did not identify any statistically significant changes of this indicator. Treatment with Acellbia® did not affect the concentration of anti-CCP, but was associated with a decrease in AMCV titres, which corresponds to data from other authors [393, 395, 396]. It is believed that a marked decrease in the concentration of RF and AMCV in RA patients receiving RTM may be due to a greater dependence of these indicators on the inflammatory activity of the pathological process as compared with anti-CCP [397]. According to our data, the concentration of anti-CCP remained stable on RTM therapy, and negative seroconversion of anti-CCP-positive results was observed mainly among patients with low-positive levels of these antibodies. One of the main immunological effects of RTM is transient, but almost complete depletion of B-lymphocytes in peripheral blood [350, 352, 358]. In our group of patients treated with Acellbia®, complete CD19+ B-lymphocyte depletion was detected by Week 12 in all patients and persisted until Week 24 in 70% of patients.

Conclusion

Therefore, the violation of B-cell immunological tolerance plays the central role in the pathogenesis of IIRDs and autoimmune diseases of another nature. B cells make the connection between innate and acquired immunity: they express Toll-like receptors that respond to danger signals; act as antigen-presenting cells; induce an antigen-specific immune response; determine the development of immunological memory; synthesize a wide range of cytokines that regulate (stimulate or depress) the immune response and inflammation. In IIRDs, there are violations of B-cell metabolism and cellular signalling, leading to defects in B_{reg}, T_{reg}, follicular T-helper cells and DC. B cells synthesize organ-non-specific and organ-specific autoantibod-

Table 14 Indications for RTM use in IIRD treatment

RA [30, 31]	ANCA-SV [31, 398, 399]	SLE [31, 109-113]	SS [237, 400]	IIM [401, 402]	SSD [403]
Administration is possible as the first-line biopharmaceutical in anti-CCP and IgM RF highly seropositive patients Other indications for administration as a first-line biopharmaceutical: • history of lymphoma • latent tuberculosis (especially if there are counter indications for chemoprophylaxis) • history of demyelinating diseases • malignancies in the past 5 years • Felty syndrome • Rheumatoid vasculitis • In in patients with TNFα inhibitor ineffectiveness, RTM administration is more appropriate than "switching" to another inhibitor of TNFα	• Remission induction in first-time patients who cannot use CP (relative contraindications): – a history of bladder tumours – premenopausal women – history of ADRs and intolerance – high risk of infectious complications? – hepatitis C? • Induction of remission in case of CP inefficiency (3–6 months) or a relapse on CP therapy • Maintenance of remission (inefficiency or poor tolerance of AZA, MT, and MMF)	• In case high activity maintains despite the use of standard treatment protocols (hydroxychloroquine and at least two immunosuppressive drugs, including MT, AZA, MMF, CP) or GC-addiction (usual GC dose of >10 mg/day depending on comorbidities and ADRs) – In case of kidney or nervous system damage it is preferable to administer RTM (if there's no such damage BLM is preferable) • In case of APS in SLE patients: autoimmune thrombocytopenia (<25•10⁹/l), despite standard therapy and in catastrophic APS	• Dry keratoconjunctivitis: if standard therapy is ineffective • Xerostomia: if standard therapy is ineffective • Systemic manifestations: CGV, arthritis, ILD, peripheral neuropathy (especially mononeuritis), lymphoma, refractoriness to GC and other immunosuppressive drugs	• In patients with ILD if standard therapy is ineffective (PRED 0.75–1 mg/kg/day) is ineffective, CP 1 g/m monthly or 1–2 g/day p/o, or CsA 3–5 mg/kg/day, or Tacrolimus 0.075 mg/ kg/day) for 6 months and CP for the next 6 months • In patients without ILD, if standard therapy is ineffective (PRED 0.75–1 mg/kg/day, AZA 2 mg/kg/day or MT 15–25 mg/week (+ folic acid) in the presence of MMT-8 count (<125) and at least two CSM indicators and occurrence of anti-synthetase antibodies (anti-Jo1, anti-Mi-2, etc.)	• Arthritis (if previous therapy with MT, GC and hydroxychloroquine was ineffective) • In case of ILD if previous MMF and CP therapy was ineffective • In calcinosis

Note. MMT – Manual Muscle Testing, CST – Core Set Measures, CsA – cyclosporine A.

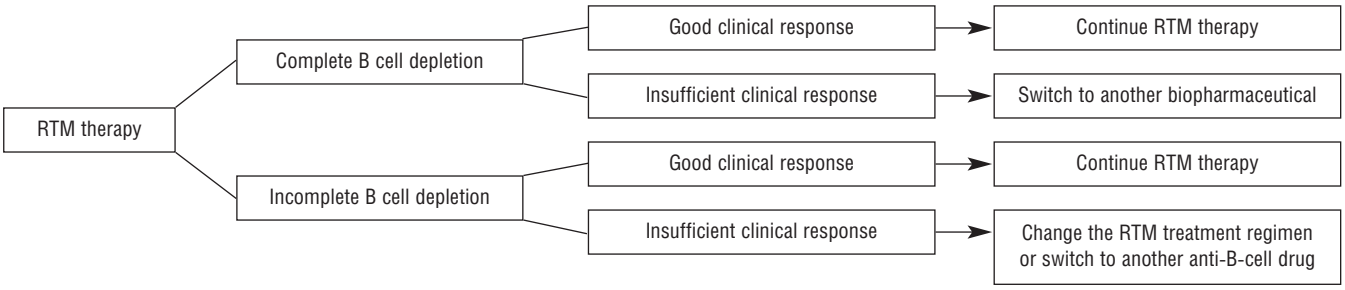

Fig. 6 Tactics of RTM use in IIRDs

ies that are markers of autoimmune diseases, and play an important role in their immunopathogenesis. Anti-B-cell therapy, which causes depression (depletion) of B cells in the blood and target organs, is effective in a wide range of autoimmune diseases. Its efficacy is determined by various mechanisms: suppression of pathogenic autoantibodies synthesis; modulation of B cells (antigen presentation, cytokine synthesis, co-stimulation), T lymphocytes, and DC functions. Anti-B-cell therapy can be considered, if appropriate, as an important component of treatment of a wide range of IIRDs (Table 14, Fig. 6), which helps to improve the prognosis for the most severe forms of these diseases. Further study of targeted anti-B-cell therapy, its mechanisms of action, and search for new targets are important for the progress of modern rheumatology, in terms of improving the strategy and harmonization of IIRD therapy.

Study transparency

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Statement of financial and other relations

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