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REVIEW

Emerging Therapies for Rheumatoid Arthritis

Joachim. R. Kalden

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ABSTRACT

Diverse strategies to develop novel treatments for rheumatoid arthritis which specifically target those patients who do not respond to available medications, including biologics, are currently being explored. New potential therapeutic approaches which may become available as part of standard therapeutic regimens include the propagation of regulatory T cells and—in the future—of regulatory B cells. New biologic disease-modifying antirheumatic drugs (b-DMARDs) against interleukin-17 and -6, granulocyte-macrophage colony-stimulating factor, and complement component 5 are now standard components of clinical treatment programs. In addition, recent data indicate that bispecific monoclonal antibody therapies may be more effective than monoclonal antibody monotherapies. It is also becoming apparent that the use of more toxic b-DMARDs against B cells, a therapeutic strategy already being applied in the treatment of hematological diseases, may also be efficacious for treating B cell-mediated autoimmune diseases. Undoubtedly, more small molecules will be developed in the future, and combination therapies with, for example, kinase inhibitors and b-DMARDs, will most likely be tested. Finally, immunoproteasome inhibitors will become available for patients with B cell-mediated autoimmunities, which are refractory to currently available treatment options. The new and exciting extension of current treatment options for rheumatoid arthritis, biosimilars, will not be discussed in this review as details on these agents are available in recently published reports.

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Joachim. R. Kalden (✉)
Division of Molecular Immunology, Nikolaus-Fiebiger-Center, Friedrich-Alexander University Erlangen–Nürnberg, Glückstraße 6, 91054 Erlangen, Germany
e-mail: joachim.kalden@uk-erlangen.de

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INTRODUCTION

The introduction of new biologic disease-modifying antirheumatic drugs (b-DMARDs) has without any doubt significantly expanded the treatment options for rheumatoid arthritis (RA) patients over the past two decades. However, the b-DMARDS currently available for treating RA patients show clinical efficacy only in about two-thirds of RA patients. In addition, some RA patients show only a partial response to treatment with b-DMARDs, and biologics are contraindicated for others. Thus, there is an obvious need to define new targets and to develop new treatment principles. Three major therapeutic avenues are discussed in this review: the activation of regulatory T cells (Tregs) or regulatory B cells (Bregs), the development of new monoclonal and bispecific monoclonal antibodies and, finally, new small molecules.

Specifically emerging therapies for RA which are already used in clinical practice or which will become available in the new future are addressed. Biosimilars, the new and exciting extension of current treatment options for RA, will not be discussed in this review as these molecules have been discussed in very recent publications. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

IMMUNE MODULATION BY TREGS

Regulatory T cells are defined as a subgroup of naïve CD4 helper T cells. They can be divided into natural Tregs (N-Tregs), which originate in the thymus, and induced Tregs (i-Tregs), which are propagated in peripheral lymphoid organs. Tregs are characterized by the expression of the transcription factor forkhead box protein P3 (Foxp3) and the surface molecule CD25. N-Tregs can be activated by interleukin-2 (IL-2), and i-Tregs are activated and expanded by either IL-2, IL-10, or transforming growth factor beta (TGFβ). An important function of Tregs is to maintain the immune homeostasis and tolerance of the host, and its main mode of action occurs via the secretion of IL-10 and TGFβ. With regard to function and phenotypic patterns, Tregs are not a homogeneous population [1–4].

The importance of Tregs in RA is underscored in a number of recent publications. It has been shown that the compromised function of Tregs T-cells in RA patients can be normalized by anti-tumor necrosis factor-alpha (TNFα) therapy [5] and that adalimumab—but not etanercept—induces a stable Treg cell population that has the potential to restrain the progression of IL-17-associated inflammation in RA via the regulation of monocyte-derived IL-6 [6]. Not only CD4-positive (CD^+) Tregs, but also CD8/Foxp3-positive ($CD8^+Foxp3^+$) Tregs have been described in RA patients. These cells can be induced by anti-CD3 monoclonal antibody and could be combined with a p38 inhibitor to improve therapeutic efficacy by resolving chronic inflammation via the restoration of tolerance. However, more data are needed to determine whether this activation of $CD8^+$ Tregs is a potentially valuable approach for treating autoimmune diseases including RA [7]. In vitro studies on the CD28 superagonist TGN14112/TABQ8 monoclonal antibody have been conducted [8–10]. When this monoclonal antibody was tested in dilutions ranging from 1 to 0.6 μg/ml on peripheral blood mononuclear cells (PBMCs) from RA patients, an expansion of Tregs was noted which was paralleled by an increase in IL-10 levels. When it was applied at

low doses to healthy volunteers, the Treg signature cytokine IL-10 was released in a dose-dependent manner in the absence of any production of proinflammatory factors [8–10]. These data contrast markedly with the results obtained when the CD28 superagonistic monoclonal antibody was administered at significantly higher doses to volunteers, with the latter developing a cytokine release syndrome [11, 12]. This superagonistic antibody is currently being tested in clinical trials in RA patients. To date, no severe side effects have been reported.

Deregulated expression of microRNA (miR)-146α and miR-155 has been associated with RA. When both of these microRNAs were studied with regard to their possible impact on Treg function, only miR-146α facilitated a proinflammatory phenotype of Treg via an increased activation of the transcription factor STAT1, thereby contributing to RA pathogenesis [13]. This finding opens the possibility to use an antagomir in those patients with this abnormal Treg phenotype. Antagomirs are a class of chemically engineered oligonucleotides which silence endogenous microRNAs.

Although the use of propagated Tregs to treat RA patients seems to be very promising, further trials are needed to definitively prove that this treatment option has the potential to be a new and efficacious treatment alternative with acceptable side effects.

NEW B-DMARDS

b-DMARDs Targeting IL-17A and IL-17R

Secukinumab has been approved by the Federal Drug Administration as a treatment for psoriasis, and approval is pending for psoriatic arthritis (PsA). Its efficacy has also been shown for the treatment of ankylosing spondylitis AS and RA. However, in RA only long-term treatment with secukinumab was associated with an improvement of signs and symptoms. More clinical data are clearly necessary to be able to reliably assess the role of blocking IL-17 A as a treatment principle for RA. Ixekizumab (Taltz®) has been shown to improve signs and symptoms of RA patients. In contrast, the human monoclonal antibody brodalumab did not show clinical efficacy in RA. In summary, it appears that the clinical signs and symptoms of psoriasis, PsA, and As in particular can be significantly improved in patients receiving b-DMARDs which target either IL-17A or the IL-17 receptor. However, for patients with RA, the clinical efficacy of this class of b-DMARDs seems to be lower than that of the TNFα blocker [14–17]. The safety profile of these new b-DMARDs is similar to that observed with other biological agents.

b-DMARDs Targeting IL-6 and the IL-6 Receptor

The first report on the use of an monoclonal antibody against IL-6 was published by Wendling et al. in 1993 [18]. After this first trial it took some time until toxilizumab came on the market, which, in contrast to other b-DMARDs introduced up to then, turned out to be an efficacious alternative treatment option in RA. Since then, quite a number of monoclonal antibodies directed against IL-6 or the IL-6 receptor have been tested in clinical trials, including sirukumab, olokizumab, sarilumab, and clazakizumab. Data from phase I to phase III trials are similar and consistent with those observed with toxilizumab [19–21]. The clinical efficacy of these b-DMARDs appears to be similar to that of TNFα blockers in patients

with the methotrexate (MTX-RI) or the TNFα receptor (TNFα-RI). Side effects include upper and lower respiratory tract infections, neutropenia, elevated enzyme levels determined in liver function tests, and elevated total cholesterol and are similar to those observed with toxilizumab [22].

Five b-DMARDs targeting IL-6 or the IL-6 receptor may soon be on the market, raising the following questions: Do we need six biologics targeting IL-6? How should these different anti-IL-6-directed b-DMARDs be used? Can they be used interchangeably such that a patient can be switched from one to the other if the first one does not show clinical efficacy? Might there be specific subgroups of patients who respond to one or the other IL-6 inhibitor preferentially? Might there be differences in long-term treatment with the different IL-6 blocking agents in terms of side effect profiles, clinical efficacy, or effect on structural damage and long-term outcome [22]. From the results available to date, it would appear that there are no major differences between these d-DMARDS targeting IL-6 or the IL-6 receptor in terms of inducing an improvement in clinical signs and symptoms and side effect profiles.

b-DMARDs Targeting IL-20

Interleukin-20 seems to be an interesting target for immune intervention in RA. IL-20 was found to be overexpressed in the synovial fluid of RA patients versus patients with osteoarthritis (OA), and IL-20 and its receptors were seen to be consistently expressed in the synovial membranes of synovial fibroblasts [23]. These results indicate that IL-20 is involved in RA, especially in local inflammation. IL-20 was found to induce the proliferation of endothelial cells. It may be involved in angiogenesis, as shown in the synovial membrane of RA patients, and it may also play a role in angiogenesis [23]. Based on this experimental data, IL-20 blockers have been used in a collagen-induced arthritis rat model as monotherapy or in combination therapy with etanercept (Enbrel). The data from these studies clearly show that in vivo treatment with the anti-IL-20 monoclonal antibody alone or in combination with etanercept significantly reduces the severity of arthritis by decreasing hind paw thickness and swelling, preventing cartilage damage and bone loss, and reducing the expression of IL-20, IL-1β, and IL-6 [24]. Available data suggest that IL-20 indeed might be a valuable target for immune intervention in RA patients, specifically when bispecific monoclonals are developed which target both IL-20 and TNFα.

EULAR recommendations for the use of biologics in RA clearly state that in all treatments biologics should be combined preferentially with MTX or, if there are contraindications, with other immunosuppressive agents [25]. This also includes treatment with tocilizumab which shows an increased clinical efficacy when given as a monotherapy as compared to when given as biotherapy with TNFα blockers [26]. In patients not showing significant response to MTX, the inclusion of tocilizumab as an add-on treatment was observed to significantly improve the signs and symptoms of RA, as well as to slow down radiological progression [27].

b-DMARDs Targeting CM-CSF

Di Franco et al. [28] recently discussed evidence supporting the development of treatments against the GM-CSF receptor in RA. These authors reported that GM-CSF has a major impact on the activation, differentiation, and survival of neutrophils and macrophages. They

observed increased levels of GM-CSF in synovial fluid, with GM-CSF exacerbating RA; furthermore, a reduction of $CD68^+$ macrophages in synovial tissue has been correlated with improvement in the disease activity score. Finally, antagonizing GM-CSF was found to markedly reduce established disease in mouse models of RA. The proof of principle that blocking GM-CSF might be a new treatment option for RA has recently been published [29, 30]. In these latter studies a significant increase in the percentage of RA patients showing a 20 or 50% response rate according to the guidelines of the American College of Rheumatology (=an improvement of 20 or 50% in signs and symptoms) was reported over a period of 24 weeks with 50 up to 100 mg mavrilimumab given subcutaneously for 12 weeks. However, further studies are necessary to determine whether this monoclonal antibody is a real alternative for patients not responding to treatment with available b-DMARDS. That GM-CSF itself might be a useful target for immune intervention in RA patients has been reported recently; in this study treatment with a human monoclonal antibody against GM-CSF was shown to be efficacious in patients with active RA [31].

Given the importance of macrophages and neutrophils for the pathogenesis of RA, one can only hope that this new b-DMARD will soon be available for use in daily clinical practice. It is important that no severe pulmonary side effects have been observed in completed or ongoing clinical trials since the epithelium of the pulmonary mucosa is a major producer of GM-CSF and GM-CSF plays a critical role locally in regulating microbial clearance and surfactant clearance by alveolar macrophages.

b-DMARDs Targeting C5

The burden of evidence supporting the involvement of complement ©) in the pathogenesis of RA has led to several attempts to apply drugs inhibiting complement activation. In this context, C5 constitutes an ideal pharmacological target: its activation leads to the release of the proinflammatory peptide C5a, a mediator involved in various immune functions, such as chemotaxis, activation of inflammatory cells, vasopermeability, among others. C5a is also essential for the assembly of the terminal membrane attack complex. An orally active C5a receptor antagonist has been shown to reduce the severity of synovitis in a rat model of immune-mediated monoarticular arthritis [32]. A novel monoclonal anti-C5 antibody, M107, has recently been described which has a high specificity for the synovial epithelium. In one study a neutralizing antibody to C5 was coupled to a peptide isolated by an in vivo selection from a phage peptide library [33]. This peptide was found to target the synovial endothelium from patients with RA and OA transplanted into SCID (severe combined immunodeficiency) mice. The peptide was highly specific, and no binding to inflamed kidney or lung was demonstrated. M107 was effective in reducing the disease severity as revealed by the decrease in joint swelling and the amelioration of synovitis [33]. More data from animal studies as well as from phase I/II clinical trials are warranted to determine whether blocking C5 will be an efficacious and alternative treatment principle for RA patients who are or become refractory to the available treatment options. Based on the animal model described here, this monoclonal antibody might be a molecule for intraarticular

application. The monoclonal anti-C5 antibody eculizumab has recently been approved for the treatment of the atypical hemolytic-uremic syndrome [34].

Bispecific Monoclonal Antibodies

Bispecific monoclonal antibodies are frequently used to treat cancer, leukemia, and lymphoma. A new bispecific monoclonal antibody, anti-CD19/anti-CD3 BITE antibody, has recently been found to be extremely efficacious for the treatment of B-cell leukemia and B-cell lymphoma due to its B-cell deleting action [35, 36]. Taking into consideration that the efficacy of rituximab, a monoclonal antibody, is also mainly due to its B cell-deleting action, an interesting question is whether the use of the anti-CD19/anti-CD3 BITE antibody could be extended to the treatment of autoimmune diseases characterized by pathogenic autoantibodies, such as RA or systemic lupus erythematosus, and specifically for those patients who do not respond to any other currently available treatments.

Recent in vitro experiments have demonstrated that the combined blockade of TNFα and IL-17 is more efficacious than a single blockade in terms of inhibiting the release of chemokines, lymphokines, or matrix enzymes. In arthritic mice, a bispecific monoclonal antibody paired on one arm to TNFα and on the second arm to IL-17 was more efficacious in inhibiting the development of inflammation and bone and cartilage destruction than either TNFα or IL-17 monoclonal antibody alone [37]. The growing interest in developing bispecific monoclonal antibodies for the treatment of RA is reflected by the increasing number of abstracts on this subject at last year's EULAR Conference. These include reports on the results of Phase-I A and Phase -II B trials conducted using bispecific antibodies against TNFα and IL-17A [38, 39] and against TNFα and ICAM-1, respectively [40], as well as data on the use of a novel dual variable domain immunoglobulin that specifically neutralizes both TNFα and IL-17A [41, 42]. The synergistic effect observed by the dual blockade of TNFα and IL17 as well as the new upcoming bispecific monoclonal antibody constructs are worth following up on, specifically to determine if they could become valuable treatment principles for RA patients.

Bispecific antibodies bind to two different antigens or epitopes on one or two different molecules at the cell surface. One of the potential advantages of these antibodies relates to their avidity. In addition, since in RA the pathogenesis is multifactorial, it is possible that a treatment which blocks two proinflammatory cytokines like TNFα and IL-6 using a bispecific antibody, or TNFα and IL-17, might be more efficacious than a treatment which blocks either IL-17 or TNFα. Finally, during the course of the disease, new and additional important pathogenic mechanisms might develop which could be attacked by bispecific monoclonal antibodies. The possibilities mentioned here may explain the known superiority of bispecific antibodies over monospecific antibodies for treatment purposes.

Regulatory B Cells

B cells are known primarily for their ability to produce both antibodies and autoantibodies for the activation of T cells via antigen presentation. B cells can also interact with and activate other cells of the immune system, such as invariant natural killer T cells via lipid antigen presentation, and they can produce a vast array of cytokines in response to a variety

or stimuli. Thus, B cell differentiation in the presence of inflammation or following priming by type 1 T helper (Th1) cells will produce high levels of proinflammatory cytokines [43]. A subset of B cells (Bregs) is capable of producing high amounts of immunosuppressive IL-10 and IL-15 [44]. Recent studies have shown that a distinct set of immunoglobulin $CD19^{+}CD138^{+}$ plasma cells are the major B-cell subsets producing these immunosuppressive cytokines during autoimmune and infectious diseases [45]. Similar to the situation regarding Tregs, specific Bregs need to be developed and tested before they can become a practicable treatment option for RA patients; specifically, the subset which produces the immunosuppressive cytokines IL-10 and IL-15 needs to be identified and tested for their efficacy in therapy.

B Cell-Targeted Therapies

Rituximab, a B-cell depleting chimeric monoclonal antibody against the CD20 protein, is a solid component of current treatment options for RA patients. Two new monoclonal antibodies against the CD20 antigen, ocrelizumab and ofatumomab, are available but not yet licensed. Whether ocrelizumab will be tested further as a possible treatment for eliminating B cells in RA patients remains at yet undetermined. Ofatumomab, which targets a membrane proximal epitope on the CD20 molecule, is distinct from other CD20 antibodies in that it has been approved for the treatment of chronic lymphocytic leukemia (CLL) [46]. The results of a clinical trial in RA patients [47] has been published, but approval for the use of ofatumomab to treat RA is still pending, awaiting the results of pivotal Phase-III studies, long-term studies, and head-to-head comparative studies with rituximab (if possible).

A Bruton's tyrosine kinase (BTK) inhibitor has recently been licensed for patients suffering from CLL. This BTK inhibitor, ibrutinib, may also be of interest for evaluation in patients with B-cell mediated autoimmune diseases [48].

The action of both tabalumab and atacicept to target B-cell survival factors has been tested, but only marginal therapeutic responses or no clinical efficacy at all were observed in RA patients [49, 50].

Based on data showing that Tregs are unable to limit B-cell responses in RA patients, the FAS pathway was identified as a possible novel target for Treg-mediated suppression of B cells [51].

Attacking the CD22 surface molecule on B cells by a sialic-acid binding immunoglobulin-like lectin (siglec) has been demonstrated to be a successful therapeutic approach for the treatment of B-lymphoma patients [52]. This new therapeutic option as well as the new monoclonal antibodies attacking the CD19 or CD319 molecules that have been introduced successfully into the treatment of plasmocytoma patients might also be used in the future for treating patients with B-cell autoimmune diseases like RA or SLE.

SMALL MOLECULES

Blocking Signaling Pathways

After two decades of often disappointing research and development, kinase inhibitors have ultimately found their way into the treatment repertoire for RA [53, 54]. It has been reported that the blocking of one or more kinases leads to a modulation of the function of different cellular structures, such as surface receptors, signaling proteins, and the

transcription of nuclear proteins, thereby influencing the behavior of the affected cell types. Tofacitinib, a drug of the Janus kinase (JAK) inhibitor class, has been approved for the treatment of RA [55–57]. Other kinase inhibitors are still under investigation in clinical trials, including baricitenib, which blocks both JAC-1 and JAC-2, and is presently being investigated in Phase-III trials. Baricitenib has additionally been demonstrated to be safe and clinically efficacious in RA patients who fail to respond to TNF-blockers [58, 59]. A JAC-1 inhibitor, ABT-494, which has been found to be effective for the treatment of refractory moderate to severe RA in two Phase-II studies, is also presently under clinical investigation [60]. Some questions concerning kinase inhibitor, however, remain unanswered: Where is the place for kinase inhibitors in our treatment repertoire: Can medications which interfere with intracellular signaling pathways be combined with other biologics? What is the long-term safety profile of molecules blocking intracellular signaling pathways?

Blocking the Proteasome

The proteasome inhibitor bortezomib, whose mode of action is to induce an unfolded protein response, has been approved for the treatment of myeloma, suggesting that inhibition of the immunoproteasome may also be an effective treatment approach for antibody-mediated autoimmune diseases.

Using the NZB/W mice model for SLE, a research group from the University Hospital Erlangen demonstrated that mice receiving bortezomib survived for a period of >70 weeks as compared to control animals who survived 50 to 60 weeks. Histology studies showed normal kidney structures in the bortezomib-treated animals, with depletion of plasma cells producing antibodies to double-stranded DNA. Even in animal models of established diseases, there was significant improvement in their clinical signs and symptoms when bortezomib was given [61]. It was shown that bortezomib specifically eliminated the so-called long-lived plasma cells in diseased organs and in the bone marrow [62]. In a first open clinical trial, bortezomib was demonstrated to be of clinical value for those SLE patients who are refractory to all other know treatment modalities [63]. Thus, bortezomib or other new proteasome inhibitors which are less toxic could become a true alternative for the treatment of RA patients and other patients with pathogenic autoantibodies.

CONCLUSION

These are exciting times for both patients and treating physicians. New compounds are being developed for treatment of RA patients and patients with other autoimmune rheumatic diseases based on the definition of new targets. This is of specific interest for those patients who are refractory to the currently available biologics. In addition to identifying new targets, researchers are exploring new avenues for therapy, such as the use of bispecific monoclonal antibodies, synerkines, or small molecules interfering with different intracellular signaling pathways. Cells like leucocytes, monocytes, macrophages, and synovial cells, including synovial fibroblasts, might be defined as valuable targets for immune intervention, including a possible intra-articular application of biologics. However, despite these new and exciting treatment developments for RA, markers to define patients who will respond to a given biologic are still missing. Such markers will give

provide the treating physician with a clue regarding to the clinical course of the disease and will improve the approach to individualized medicine.

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