New therapeutic approaches in rheumatoid arthritis

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Summary

The treatment of rheumatoid arthritis (RA) has changed dramatically over the past two decades. The combination of better insights into the pathophysiological and immunological mechanisms of RA and the possibilities offered by biotechnology led to the development and introduction into clinical practice of a new class of antirheumatic biologic therapies, which along with earlier and more aggressive treatment contributed to dramatically better outcomes for patients with RA. To date, nine biologic agents have been approved for the treatment for RA, and a first Janus kinase (JAK) inhibitor has also been approved in the United States and various other countries in the world (but not by the European Medicines Agency [EMA]). Many additional molecules with distinct mechanisms of action are currently being tested in laboratories and in clinical trials. In addition, considerable improvements have been made in the optimal use of all these agents through treatment strategies such as treating-to-target, induction-maintenance, and dose individualization.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic disease of the joints characterized by synovial inflammation that can lead to cartilage and bone destruction. The disease is associated with various extra-articular inflammatory complications (scleritis, pleurisy, vasculitis) and often features systemic inflammation as well. RA is generally thought to be autoimmune in nature, and it is believed that genetic predisposition (HLA-DR4 and the “shared epitope”) and environmental factors (smoking, certain exposures) interact to bring about the full-blown disease. RA occurs in all age groups and has an overall prevalence of around 0.8% in Europe; the incidence peaks around the fifth decade of life and women are affected three times as often as men.

When left untreated, RA usually has a chronic course characterized by undulating pain and stiffness as well as general malaise, and it may also cause progressive destruction of cartilage and bone in the joints (figure 1), resulting in typical deformities, loss of function, and handicap. Treatment for RA is therefore based on the dual principle of controlling the inflammatory process so as to provide relief of symptoms for the patient, and preventing the destructive process so as to preserve...
functional status. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) may provide the first but not the second of these objectives, and therefore it is generally held that RA should be treated with proper antirheumatic medications. These medications, usually referred to as conventional disease-modifying antirheumatic drugs (DMARDs), are a small group of chemically unrelated compounds that have been shown to achieve at least some degree of both symptom control and prevention of damage progression. The most widely used DMARDs are methotrexate (MTX), an antimetabolite with powerful anti-inflammatory effects that are possibly mediated through the local release of adenosine, sulfasalazine (SSZ; figure 2), and leflunomide.

**New treatments for RA**

Over the past two decades, a whole new class of antirheumatic biologic therapies or biologic DMARDs (bDMARDs) has been introduced into the clinic, based on better insights into the pathophysiological and immunological mechanisms of the disease and the possibilities offered by biotechnology. These drugs, along with earlier and more aggressive treatment, brought about a true revolution in this therapeutic area with major improvements in the outcomes of the disease. To date, nine biologic agents have been approved for the treatment for RA (figure 3), and a first Janus kinase (JAK) inhibitor, a small-molecular compound with biologic-like efficacy, has also been approved in the United States and various other countries in the world (but not by the European Medicines Agency [EMA]). Many additional molecules with distinct mechanisms of action are currently being tested in laboratories and in clinical trials. The approved biologics were shown to have very good clinical efficacy and safety in large, randomized, controlled clinical trials leading to regulatory approval; and biological therapies for RA have become widely used and have been intensively studied. The approved biological treatments include five tumor necrosis factor inhibitors (TNFi) and four agents with other mechanisms of action (figure 4).
Tumor necrosis factor (TNF; formerly designated TNF-α) is a cytokine of central importance in multiple inflammatory processes and is among the dominant cytokines in the inflamed synovium of RA patients [1,2]. To date, five unique anti-TNF agents are used in rheumatology practice and a biosimilar anti-TNF has also been approved in Europe.

**Infliximab (Remicade)**
It was the first anti-TNF to be tested, first in investigator-initiated clinical trials and then in the large Attract trial [3], which demonstrated outstanding efficacy and good safety. Later trials also demonstrated efficacy for infliximab in early RA [4], and infliximab was the anti-TNF used in a large number of investigator-initiated clinical trials done over the past decade [5-7] (figure 5). The safety and tolerability of infliximab were studied in all these clinical trials and in many large observational registries. The infusion itself may be associated with infusion reactions. During the first years of the clinical use of infliximab severe infusions reactions were not infrequently seen, and units providing infusion treatments had to be equipped to deal with these. Remarkably, the frequency of severe infusion reactions has shown a dramatic decline over the years [8], and it seems reasonable to speculate that improved production methods of the biological compound are to be credited. Treatment with infliximab, as with all anti-TNF agents, increases the general risk of infections but the absolute risk increase is quite small and mostly seen in the first year of treatment [9]. In contrast, certain specific infections show more strikingly increased risks, tuberculosis (tb) being the most important one where the risk of reactivation of latent tb is greatly increased. For all anti-TNF agents (and in fact for all biologics), screening for latent tb is required, and such vigilance has clearly shown to decrease the incidence of reactivation of latent tb. While the risk for cancer in general does not seem to be increased with anti-TNF treatment, a meta-analysis of early clinical trials suggested a slightly increased risk of non-melanoma skin cancer with infliximab and adalimumab, particularly at higher dosages [10], and a more recent study suggests a very small but measurable increase in the risk for melanoma [11]. All anti-TNFs may rarely trigger other autoimmune diseases such as psoriasis and demyelinating disease, and lupus-like syndrome. Fortunately, all of these are usually mild and reversible.

**Etanercept (Enbrel)**
It was one of the first two approved anti-TNF treatments. It was genetically engineered by coupling the two copies of the naturally occurring p75 TNF-receptor to an IgG framework, yielding a
bivalent TNF-binding molecule with similarities to monoclonal antibodies but also some differences. Rather small pivotal trials with etanercept during the 1990s showed convincing efficacy compared to placebo both as monotherapy and in combination with MTX [12, 13]. A trial in early RA showed that etanercept was similarly efficacious to MTX but with a faster onset of action and better slowing of radiological progression [14]. Following approval, the Tempo trial demonstrated that the clinical efficacy of etanercept combined with MTX was most effective, particularly at achieving “high-end” outcomes such as the ACR70 or DAS28-defined remission [15]. In the recent Preserve trial [16], patients who achieved sustained low disease activity with etanercept after 36 weeks were randomized to one of three arms: those who continued only MTX (plus placebo), those who continued MTX plus etanercept at reduced dose (25 mg weekly) and those who continued both medications at the original dose. After an additional 52 weeks more than half of the patients on MTX alone had worsened and no longer had low disease activity. In contrast, in both groups who had continued with etanercept the vast majority maintained low disease activity without a difference between the two doses. Similar results were seen in the Dosera trial [17]; and the Prize trial [18] in patients with early RA showed that continuing etanercept at half dose (25 mg weekly) maintains the favorable response in a majority of cases (63%), whereas MTX alone does so in 40%. The safety of etanercept throughout the clinical trials program was very good and later studies confirmed a relatively low incidence of side effects, including injection-site reactions. Some of the trials suggest that mild respiratory infections are more common with etanercept, and a slightly increased risk for serious infections has emerged as discussed above [9]. The risk for reactivation of latent tuberculosis, which was demonstrated clearly for anti-TNF monoclonal antibodies, may also be elevated with etanercept but there has been a consistent impression throughout many observational studies that the risk may be smaller with etanercept than with the other anti-TNF medications. The approved dose of etanercept is 50 mg weekly as a subcutaneous injection; the earlier dosing of 25 mg twice weekly is also still sometimes used. From the above trial results, it has become clear that a lower “maintenance” dose, while not approved, may be sufficient for many patients.

**Adalimumab (Humira)**

It is a fully human anti-TNF monoclonal antibody. In a large phase III program, in patients with incomplete response to methotrexate (MTX) the addition of adalimumab demonstrated clinical responses that were significantly better than placebo with a dose optimum at 40 mg every other week [19]; and as monotherapy with a small additional benefit (not statistically proven) for 40 mg given weekly [20, 21]. As had previously been demonstrated for other anti-TNF agents, the combination of MTX and adalimumab proved to be highly effective at preventing the progression of radiographic damage. Both the efficacy data obtained from randomized clinical trials and safety data obtained from both trials and observational studies are very similar for adalimumab compared to the first two anti-TNF agents, etanercept and infliximab. As has been seen for etanercept, some recent studies suggest that lower dosages of adalimumab may be adequate for maintaining clinical responses once they have been obtained.

**Certolizumab pegol (Cimzia)**

It is one of two more recently approved anti-TNF agents. It consists of an anti-TNF Fab’ fragment linked to polyethylene glycol (PEG) molecules for longer half-life. Clinical trials...
demonstrated convincing efficacy for certolizumab over placebo [22-25]. Safety aspects with certolizumab were largely similar to those seen with other anti-TNFs. The incidence of tb and other infections during the clinical trials with certolizumab was somewhat higher than in the placebo groups, but comparable to that seen with other anti-TNF agents. A systematic review appeared to show higher risks for infection with certolizumab compared to the other TNF inhibitors [26], but weaknesses in the analyses and major differences between the various trials make it plausible that a true difference is very small, if one exists at all. Certolizumab is approved as a single biweekly subcutaneous 200 mg injection or alternatively as two injections given every four weeks (the same total dose) in patients on background MTX; only the latter dose is approved for monotherapy.

**Golimumab (Simponi)**

It is a fully human anti-TNF monoclonal antibody. Its most notable clinical feature is a long dosing interval, having been approved as a subcutaneous injection once a month. The clinical efficacy of golimumab was demonstrated in an extensive phase III clinical trial program, where it was shown that the drug provided very good clinical efficacy at several dosage levels in various patient groups [27-29]. One of these trials was done in patients who had already failed another anti-TNF agent and golimumab therefore is the only anti-TNF that has proven efficacy in that patient population [30]. The radiological benefits of golimumab were not demonstrated as clearly as was the case for some of the original anti-TNF agents. However, it has been recognized that the demonstration of radiological benefit in clinical trials has become progressively harder. Risks and side effects with golimumab do not seem to differentiate from other anti-TNF agents. Thus, screening for latent tuberculosis is mandatory, and the frequency of other infections may in general be slightly increased. Golimumab is approved at a dose of 50 mg subcutaneously once a month. The double dose, 100 mg, is also approved and may confer additional benefit. In clinical trials, golimumab given intravenously was shown to be effective and well-tolerated [31], and intravenous golimumab (Simponi Aria) was approved by the FDA.

**Infliximab biosimilars**

The first infliximab biosimilar for the treatment of RA was approved by the European medicines agency (EMA) in 2014, on the basis of a single randomized double-blinded trial that demonstrates that it was equivalent in its clinical effects to infliximab-Remicade in RA [32]. This product is marketed under two different names: Inflectra and Remsima. The impact of the approval of a biosimilar on the rheumatological therapy landscape has yet to be seen. It is important to recognize that the pricing difference between a biosimilar and its originator will not be as dramatic as can sometimes be the case for generics of conventional pharmaceutical products, in part because biologics come with very high costs for the production itself, but also because in the economics of the pharmaceutical marketplace the number of patients that will be treated with a drug is clearly one of the determinants of pricing. Although the rheumatological indications are important and not uncommon, they are clearly at a different level from anti-hypertensives and statins. So far, the price of biosimilar infliximab has been roughly half of the price of the originator, but with wide variability between countries.

**Biologics with other mechanisms of action**

**B-cell depleting therapy: rituximab**

Rituximab (Mabthera, Rituxan) is a chimeric monoclonal antibody directed against the CD20 molecule which is present on all mature B-cells, and was originally approved for the treatment of non-Hodgkin lymphoma. Following infusion of rituximab, complete depletion of B-cells from the peripheral blood can be documented within a matter of days. Randomized trials with rituximab in RA demonstrated excellent efficacy when given either as monotherapy or in combination with MTX [33]. These trials included patients who had failed treatment with at least MTX but in most cases also with at least one anti-TNF agent, and responses were numerically comparable to those seen with anti-TNF in trials [34,35]. Rituximab was also shown to slow radiological progression [36]. The safety profile of rituximab has been remarkably benign considering the profound B-cell depletion it causes. Infusion reactions are sometimes seen but they are rarely severe. Nevertheless, premedication with glucocorticoids is recommended with rituximab infusions and the infusion site has to be equipped to deal with severe reactions. Also, a delayed infusion reaction, occurring 7-14 days after infusion and resembling “serum sickness” has been seen in some patients. In controlled trials, the frequency of infections following rituximab was not markedly elevated, and long-term follow-up of patients in clinical trial extension programs has not revealed any unexpected safety concerns [37]. In post-marketing spontaneous reporting a small number of cases emerged of progressive multifocal leukoencephalopathy (PML) [38]. The absolute risk is very small, in the order of one in 20,000. The approved rituximab dosage is 1000 mg given intravenously twice with two weeks in-between, and this "course" can then be repeated. In practice, repeat courses are often given when disease activity recurs, but some studies suggest that it is advantageous to schedule six-monthly repeat courses as a standing order. There is some uncertainty regarding the optimal dosing since the phase III trial program in effect only tested one dosage. Both randomized trials and observational studies strongly suggest that a course consisting of 500 mg given twice, or possibly 1000 mg given once, is just as effective as the approved dosage [18,34,39,40]. The pharmacoeconomic benefit of using the lower dose is obvious. Rituximab is usually given on a MTX background but has also been used as monotherapy or in combination with other DMARDs. While the monotherapy...
seems slightly less effective, one large observational study suggested that the combination of rituximab with leflunomide may be even more effective than the one with MTX [41].

**T-cell costimulation antagonism: abatacept**
The Abatacept (Orencia) is a construct of the naturally occurring CTLA-4 molecule coupled to an IgG framework. It interferes with the "second signal" and thereby down-regulates T-cells. Several trials confirmed that abatacept has good clinical efficacy in the treatment of RA in different stages of the disease [42]. Thus, efficacy that was comparable to anti-TNF was demonstrated in patients who had an incomplete response to MTX [42], and good clinical efficacy was also demonstrated for patients who had previously failed anti-TNF [43]. Abatacept was also shown to inhibit radiological progression [44,45] and to be effective in early RA [46] and even in very early undifferentiated arthritis [47]. A head-to-head comparison with adalimumab, when both were given in combination with MTX, showed almost identical efficacy for the two agents [48]. The very recent Avert trial in early RA confirmed that abatacept + MTX was more effective in early RA than either drug alone [49]. The safety profile of abatacept in clinical trials has been very favorable. Small increases of infections and other minor adverse events have been seen as with all immunomodulatory agents, but this treatment does not seem to be associated with major risks. Screening for tuberculosis is recommended but in fact the risk for reactivation of latent tuberculosis has not been demonstrated. Abatacept is given as an intravenous infusion at a dosage of 500–1000 mg based on body weight every four weeks or subcutaneously at 125 mg weekly. The two forms of administration have formally been shown to be equivalent [50] and choosing between them is mostly a matter of preference.

**Tocilizumab (Actemra/Roactemra)**
It is a humanized monoclonal antibody that targets the IL-6 receptor (IL-6R) so that the pro-inflammatory signal mediated by IL-6 is prevented. In large randomized double-blinded trials, the drug was shown to be effective in patients who had an incomplete response to MTX [51] or to other DMARDs [44,52,53], in patients who had an incomplete or no response to an anti-TNF agent [54], and in patients who had not yet been treated with MTX [55]. In each of these trials, two dosages of tocilizumab were tested: 4 mg/kg and 8 mg/kg, each given every four weeks. The clinical efficacy of both dosages compared to placebo was excellent, numerically comparable to that seen in similar trials with anti-TNF. One trial was designed specifically to investigate the radiological efficacy of tocilizumab and demonstrated significant slowing down of radiological progression [56]. Following approval of the drug, some additional clinical trials were done with interesting results. In the Adacta trial, [57] tocilizumab was slightly but significantly better than adalimumab monotherapy. In several trials [58–60], it was shown that subcutaneously administered tocilizumab is similarly effective and safe when compared to the intravenous form, resulting in the subcutaneous formulation being approved for use both in the US and in Europe. The safety profile of tocilizumab (and other IL-6 antagonists) reveals some similarities but also important differences with anti-TNF agents. More specifically, just as is the case for most immunomodulatory therapies there is a small increase in infections, and a long-term effect on the risk for cancer cannot be excluded. Reactivation of latent tuberculosis has occurred and screening for (latent) tuberculosis is mandatory. There are also several adverse events and risks that differentiate between anti-IL6 and other biologics: elevated transaminases occur at a higher frequency with tocilizumab than with other agents and can in some instances be severe, although outright hepatic failure did not occur in the clinical trials program. This kind of risk necessitates close monitoring of the patient with blood tests, and it should be emphasized that the absence of more severe consequences (liver failure) in the clinical trials is seen in the context where patients are closely followed. Cytopenias, particularly leukopenia, neutropenia, and also thrombocytopenia occur with tocilizumab therapy and can sometimes be severe, necessitating monitoring during therapy. In the clinical trial program, no or very few consequences were noted of these laboratory abnormalities, but in the clinical trial setting patients are closely monitored through blood tests and if or when abnormalities are noted prompt and specific action is mandated by the protocol. A consistent increase in serum cholesterol levels is seen in patients treated with anti-IL6 agents. The increase is seen in both LDL and HDL cholesterol, yielding a stable or only slightly changed atherogenic index. The long-term consequences of these lipid alterations are not known. In the long-term safety follow-up of patients who originally participated in the clinical trials, there was no increase of cardiovascular events [61]. The production of C-reactive protein by the liver is stopped almost completely when IL-6 is blocked; it is important for health-care providers to be aware of this issue, particularly in the acute-care setting. Tocilizumab is approved at either 4 or 8 mg/kg given intravenously at four-week intervals, and subcutaneously at 162 mg given once weekly.

**Interleukin-1 antagonism: anakinra**
The naturally occurring interleukin-1 (IL-1) receptor antagonist (IL-1RA) is believed to help in controlling the physiological inflammatory response. IL-1RA was cloned and became one of the first biological agents, anakinra (Kinereit). In a large clinical trial program in RA, the results suggested good efficacy [59,62–65]. Eventually the drug was approved for the treatment of RA, but results in practice were disappointing. Data from clinical trials suggest somewhat less robust responses with anakinra, and the onset of action may be slower – however, no head-to-head trials have ever been performed. It is also
possible that one of the main reasons for the failure of anakinra in RA therapy had to do with the inconvenience of daily subcutaneous injections, something few patients with RA are prepared for; and perhaps even more so, the frequency of quite severe cutaneous reactions to the drug. At present, there is only a limited role for IL-1 antagonism in the treatment of RA.

**Novel biologic agents targeting the IL-17/IL-23 axis**

The discovery of the important role of the Th17 lymphocyte and the cytokines IL-17 and IL-23 in the inflammatory process has prompted the development of various new biologic agents with these targets. Several of these agents have demonstrated excellent efficacy in psoriasis and also in many cases efficacy in psoriatic arthritis (PsA). In contrast, results from studies in RA have generally been less impressive, and it is unclear to what extent these agents will have a place in the RA treatment armamentarium.

**Ustekinumab (Stelara)**

It is an IL-12/23 antagonist. Because IL-12 and IL-23 share a common chain, they can be targeted by a single monoclonal. Ustekinumab was tested in various autoimmune diseases and was approved for psoriasis after phase III trials had given good results in this skin disease [66]. Ustekinumab is currently a respected biologic agent in dermatology for use in patients with psoriasis who are in need of systemic therapy, usually in those who have already failed methotrexate and/or an anti-TNF biologic. A direct comparative trial suggested that it might be more effective than etanercept (given at the high psoriasis dose of 50 mg twice weekly) [67]. More recently, ustekinumab has also been approved for the treatment of psoriatic arthritis (PsA) on the strength of trials demonstrating efficacy over placebo [68-70]. The absolute magnitude of the responses in these trials may be somewhat less than those seen with anti-TNF biologics, but no direct comparisons are available. There are no published trials of ustekinumab in RA.

**Secukinumab**

Secukinumab binds to IL-17A and neutralizes its activity. It has been shown to be effective in psoriasis [71], PsA [72] and ankylosing spondylitis [73]. A phase II trial in RA using a range of dosages did not achieve its primary endpoint but modest efficacy over placebo was seen in several outcomes [74].

**Ixekizumab**

Ixekizumab binds and neutralizes both IL-17A and IL-17F. It is very effective in psoriasis [75] and has been tested in trials for PsA and ankylosing spondylitis. A small phase I and a larger phase II trial suggested moderate efficacy in RA [14,76,77].

**Brodalumab**

Brodalumab targets the IL-17 receptor A and has been found very effective in psoriasis [78-80] and PsA [81]. In RA, one small trial did not suggest efficacy [82]. Recently, one of the two companies that develop brodalumab announced that is discontinuing the development, citing concerns over suicidal ideation in some patients in the trials, so the future for this compound is unclear.

**GM-CSF antagonist: mavrilimumab**

The monoclonal antibody mavrilimumab targets the granulocyte-monocyte colony stimulating factor GM-CSF which in addition to its role in hematopoiesis has important immunoregulatory functions as well. The monoclonal showed convincing efficacy and good tolerability in a large phase II trial in RA [83].

**Other IL-6 antagonists**

Several other monoclonals targeting the IL-6 pathway are currently in development for RA and other diseases. Sarilumab is a fully human monoclonal that binds to the IL-6R in a manner similar to tocilizumab. It appeared effective and safe in a phase II study in RA population [84]. Sirukumab, an anti-IL6 monoclonal antibody, was also effective and safe in a recently published phase II trial [85], as were olokizumab, a humanized anti-IL6 monoclonal antibody [86], and clazakizumab [87]. All these agents appear similarly effective and safe as tocilizumab.

**Janus kinase inhibitors**

Janus kinase inhibitors

Since the first outstanding results with biologics were reported it has been speculated that small-molecular agents could be developed with the same effects. Unfortunately, years of pharmacological development led to many failures in this regard, the development of p38 MAP kinase inhibitors being an example [88]. However, the development of small-molecular agents that target the Janus kinases (JAKs) and perhaps some other intracellular enzymes has opened a new chapter in therapeutics for RA with small-molecular medications whose efficacy is comparable to biologics. The Janus kinases are a small group of four different intracellular enzymes that belong to the large family of tyrosine kinases and that are intimately involved in the cellular activation that occurs after any of a large number of cytokines binds its receptor on the cell surface. Several inhibitors of JAKs have been developed as potential treatments for RA; currently one is approved while several others are in clinical development.

**Tofacitinib (Xeljanz)**

It selectively blocks JAK1 and JAK3 and leads to decreased intracellular activation upon binding of many cytokines including interferons, IL-2, -4, -6, -15, -21, and -12/23. In a very large phase III clinical trial program, it was shown to be clinically efficacious for the treatment of RA both in combination with MTX

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transaminase elevations were seen in almost one fourth of patients and were sometimes severe. Likewise, cytopenias were seen frequently and sometimes reached high levels. These laboratory abnormalities did not, however, lead to major events, and while this is reassuring it should be emphasized that this is almost certainly due to the fact that the patients were monitored closely and that laboratory abnormalities led to protocol-specified actions on the part of the investigators to minimize risks. In the RA trials, tofacitinib was associated with a small but consistent increase in creatinine, the cause of which is not clear. Tofacitinib also predictably results in increases in cholesterol, both LDL and HDL. The long-term consequences of this are not known. Tofacitinib was approved by the U.S. FDA and by most other drug authorities in the world, but not by the EMA. The U.S. approval is for the 5 mg dose orally twice daily, and it can be used as monotherapy or in combination with MTX or other DMARDs.

**Other JAK inhibitors in development for RA**

Baricitinib is a JAK antagonist with specificity for JAK1 and JAK2. In a phase II trial, it has shown very good efficacy, comparable with biologics and with tofacitinib [94]. Acceptable safety was also demonstrated and the a priori concern that JAK2 inhibition would result in high rates of anemia was not confirmed. A large phase III program has been initiated and the first results were recently presented at the international congress of the European League Against Rheumatism (EULAR). Primary and secondary endpoints of these studies were met and no new safety concerns have emerged. Decernotinib (VX-509) is a JAK inhibitor with high selectivity for JAK3. Phase II trials have confirmed efficacy [95]. Interestingly, another JAK inhibitor, filgotinib is highly specific for JAK1 and this compound, too, demonstrated very good efficacy in RA according to recent press releases. If confirmed, the overall findings of efficacy with a range of JAK inhibitors of varying specificities suggest that the specificity profiles of these agents may not be as critically important as was originally believed. It is possible that the activation pathways downstream from the JAKs have more “cross-talk” than had originally been recognized. Additional JAK inhibitors are in earlier-phase trials.

**The spleen tyrosine kinase (Syk)**

It is another intracellular enzyme involved in cellular activation following binding of the B-cell receptor. Early-phase trials with the Syk-antagonist fostamatinib suggested efficacy [96] but later trials did not confirm this [97,98] and the development has been terminated. The selective inhibitor of phosphodiesterase 4 (PDE-4) apremilast (Otezla) was recently approved for the treatment of psoriatic arthritis. Although it has shown in vitro activity on RA synovial cells [99], no trials in RA have been published.

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**Figure 6**

Clinical responses over time [93]

An American College of Rheumatology (ACR) 70 response is defined as at least a 70% reduction from baseline in the number of both tender and swollen joints, as well as at least a 70% improvement in three of five other criteria: the patient’s assessment of pain, level of disability, C-reactive protein level or erythrocyte sedimentation rate, global assessment of disease by the patient, and global assessment of disease by the physician. The coprimary end point (the ACR 70 response at month 6) was derived from the prespecified interim (year 1) data set; the ACR 70 response over time was derived from the final (year 2) data set. Missing data were imputed with the use of nonresponse imputation. I bars indicate standard errors. Asterisks denote P < 0.001 for the comparison with methotrexate.
Activation of regulatory T-cells

An entirely different conceptual approach to autoimmunity would be the activation of regulatory T-cells (Tregs). Extensive animal experience suggests the feasibility of this approach, but human trials have run into difficulties. The activating anti-CD28 monoclonal TGN1412 caused severe side effects in its first-in-man trial, clearly caused by the widespread activation of inflammatory pathways [100]. This episode delayed further developments in this direction by many years. However, more recently the monoclonal antibody tregalizumab which is directed against a specific epitope on the CD4 molecule was shown to activate Tregs only [101] and was safe in phase I trials in healthy volunteers. A small trial in RA suggested possible efficacy and a large trial in RA was recently completed. Unfortunately, according to a recent press release the primary endpoint in this trial was not achieved. Nonetheless, if Tregs could be harnessed to control one autoimmune disease such as RA, it would suggest additional applications in many other autoimmune diseases as well.

New treatment strategies in RA

Treating-to-target

In addition to ongoing efforts to identify better therapeutics for RA, the reevaluation and reassessment of treatment strategies for RA will continue and may lead to entirely new treatment paradigms. The principle of treating-to-target was originally derived from diseases such as hypertension, where trials demonstrated that long-term outcomes were better if clinicians clearly identified the blood pressure that they wanted to achieve and took action to achieve it. For rheumatoid arthritis, at least two randomized trials also provided direct evidence that such an approach, based on targeting a certain level of the disease activity score (DAS), yielded better long-term results [102,103]. Formal treat-to-target (T2T) guidance for RA was published several years ago and the principle has increasingly been implemented [104]. Similar recommendations have also been developed for several other rheumatic diseases [105,106]. It should be emphasized that T2T is not only about choosing a target, but also about deciding on how and when to measure that target and about the principle that failure to achieve the target should lead to a therapeutic change in most cases.

Induction-maintenance

The large Optima trial demonstrated that patients who are started on treatment with MTX + adalimumab and who have a very good response can often be continued on MTX alone and maintain the same good response [107]. Similar results were more recently seen in the Preserve [16] and Prize [18] clinical trials with etanercept, and the Avert trial showed that a very small proportion of patients could achieve a durable remission without any treatment following induction with MTX plus abatacept [49], a finding that is perhaps more scientifically important than clinically applicable. But based on these and other trials, it is possible to speculate that in the future it will be acceptable to initiate treatment with a biologic in combination with MTX for patients with newly diagnosed RA with the intention to discontinue the former once a stable low disease activity status or remission has been achieved.

Dose individualization

While some biologics are approved as a single "one-size-fits-all" dosage, for others a range of doses is available, most notably for infliximab (3 to 10 mg/kg), adalimumab (40 mg weekly or biweekly), and golimumab (50 or 100 mg monthly). This is often interpreted as an option for patients who on the lower dose do not achieve a satisfactory response, whereby a dose or frequency increase can result in a better clinical outcome. However, this may not be the case. For infliximab, a randomized trial failed to demonstrate a benefit for a dose increase from 3 to 6 mg/kg [108] and in the Premier trial the weekly dose was not superior to biweekly [109]. For the clinician, it may be hard to resist the temptation for dosing-up (if the drug reimbursement system does allow it) but there may be additional safety issues with the higher dosages [10]. Thus, dosing-up should be done only under compelling circumstances and with a strict intention to monitor the results closely.

Dosing-down, on the other hand, has become a topic of considerable interest, as several recent trials have suggested that this may indeed be a possibility for several biologics. Some of these trials have focused on patients with newly diagnosed RA and have been discussed above under the heading of induction-maintenance. But even in patients with established RA some recent trials have evaluated the possibility of dosing-down in...
patients with a stable disease state of low activity or remission. Thus, in the DRESS trial [110] and the STRASS trial, a large majority of patients were able to increase the dosing intervals for etanercept and adalimumab while maintaining a low disease activity state, and in a separate study it was suggested that the same could be true for patients on tocilizumab [107,111].

**Conclusion**

In summary, the treatment of RA has undergone dramatic changes over the past twenty years. From having only limited means to provide some measure of relief, rheumatologists can now feel confident that for many patients with this disease reasonable disease control can be achieved. Through further development of additional antirheumatic therapies and through the implementation of better treatment strategies, further improvements will be achieved, and patients will continue to do better.

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**References**


New therapeutic approaches in rheumatoid arthritis


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