Review

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The future of biological agents in the treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease with a currently unknown etiology and multifactorial pathogenesis. This review recaps on the history of development of the main principles of biological disease-modifying agents. Moving into current treatment guidance from Europe and the USA, monotherapy and second-line biological choice is addressed. The reviews explores and summarizes the latest developments and potential impact of anti-cytokine therapy, including TNF, IL-6 and IL-17, anti-lymphocyte therapies, B cell modulators and other B-cell targets, anti-CD3, biosimilars and finally oral agents such as JAK and Syk inhibitors.

Keywords: biologic • disease-modifying antirheumatic drugs • JAK inhibitor • rheumatoid arthritis • TNF inhibitors

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What is rheumatoid arthritis & what are biological agents?

Rheumatoid arthritis (RA) is an autoimmune disease with a currently unknown etiology. The pathogenesis is multifactorial and complex. Synovial inflammation causes joints to be hot, swollen, stiff and painful with the small joints of hands and feet usually being affected first. Synovial cell inflammation and hyperplasia are early events in the pathologic process that progresses to cartilage and bone destruction [1]. RA inflammation and proliferation of the synovium (called pannus), leads to destruction of bone and cartilage. If the inflammation goes on without treatment, it can lead to joint damage and may lead to loss of functional capacity. Once the joint is damaged it cannot be repaired, so treating RA early is the target. Although the articular structures are the primary sites involved by RA, other organs are also affected with extra-articular manifestations including secondary Sjogren syndrome, pulmonary fibrosis, renal amyloidosis and cardiovascular disease [2,3].

Genetic and environmental factors contribute to disease development. Genetic studies in RA twin studies have a concordance rate of 15–30% [1], the strongest of which is associated with HLA-DRB1. Another loci of recent interest is PTPN22, which appears to predispose to autoimmunity. Intermingled with genetic predisposition, environmental factors such as smoking and possibly coffee, are also thought to play a role. Infections (Epstein–Barr virus [EBV], cytomegalovirus, parvovirus B19 and *Porphyromonas gingivalis*) are candidates for the trigger of autoimmunity but no clear link has yet been shown. With autoimmunity affecting mainly women, thought has also turned to whether hormones or reproductive factors stimulate disease. Association has been found between increased severity of disease and older age at menarche, and multiparity, pregnancy itself being a risk factor for disease with 12% of women suffering the onset of RA within a year of pregnancy.

Treatment options for RA have dramatically transformed in the last 20 years with more target-specific therapy. Unfortunately, this revolution of discovery comes at a cost. Increasing therapeutic options and growing populations makes competition fierce and attention needs to be turned to health as well as cost-effective solutions for the future.

Future Medicine part of fsg

Both the innate and adaptive immune responses are involved in the destructive rheumatoid process. T and B cells, antigen-presenting cells, monocytes and cytokines have all been implicated. It is thought that $CD4^+$ T-helper cells may initiate the disease process in RA. These cells produce IL-2 and IFN-γ cytokines when activated by an antigen-presenting cells. IL-2 and IFN-γ may go on to activate macrophages and other cell populations, including synovial fibroblasts. Macrophages and synovial fibroblasts are the main producers of TNF, IL-6 and IL-1. Aberrant production and regulation of both proinflammatory and anti-inflammatory cytokines and cytokine pathways are found in RA. Experimental models suggest that synovial macrophages and fibroblasts may become autonomous in the presence of a proinflammatory cytokine network leading to chronic inflammation.

B cells are important in the pathologic process and may serve as antigen-presenting cells. B cells also produce numerous autoantibodies (e.g., rheumatoid factor) and secrete cytokines. Antibodies that form immune complexes can activate complement cascade and cause tissue damage.

Treatment of RA

Medications for RA target the reduction of inflammation thereby improving symptoms and preventing joint damage. There are three main groups of medications in RA: NSAIDs, corticosteroids and disease-modifying antirheumatic drugs (DMARDs). Several studies [4–6] have provided evidence that early treatment with DMARDs results in superior clinical and radiological outcomes. DMARDs are divided into two categories: synthetic DMARDs and biologic DMARDs. Synthetic DMARDS, such as methotrexate (MTX), hydroxychloroquine, leflunomide and sulphasalazine, are cheaper and are normally used as a first line. Biologic DMARDs are often used when synthetic DMARDs fail to control RA. Development of biologic DMARDs resulted from identifying 'therapeutic targets' that may be responsible for driving inflammation. Monoclonal antibodies or immunoconstructs can then be developed for these targets. The first successful target was the cytokine, TNF. Marc Feldmann and Ravinder Maini formulated their hypothesis implicating TNF in the pathogenesis of RA in the 1980s [7]. Subsequent clinical trials using infliximab, a chimeric anti-TNF monoclonal antibody, and the immunoconstruct etanercept, confirmed the importance of TNF in RA and led to the license approval of these biologic DMARDs for RA. Since then, five different classes of biologic agents have been developed and tested (see Table 1).

TNF inhibitors are the most commonly used biologic DMARD for RA. TNF is known to be responsible for endothelial cell activation, the induction of metalloproteinases and adhesion molecules, angiogenesis, regulation of inflammatory cytokines, bone erosion and fibroblast, keratinocyte and enterocyte activation. Reduced expression of adhesion molecules and cellularity in the RA synovium after TNF inhibition, may support that the anti-inflammatory effects could be partly explained by downregulation of cytokine-inducible vascular adhesion molecules in the synovium, with a consequent reduction of cell traffic into joints [8]. Circulating levels of IL-1 and IL-6 are also decreased after treatment. Upon TNF blockade, angiogenesis is also significantly reduced and lymphangiogenesis increased.

Etanercept, the second biological agent licenced for RA in 1998, is a soluble p75 TNF receptor fusion protein that is made up of two TNF receptors. These are bound to the Fc portion of IgG, therefore bivalent binding two TNF molecules per etanercept molecule.

Infliximab was closely followed by adalimumab and golimumab, two fully human anti-TNF antibodies. Similarly, polyethylene-glycolated Fab' fragment with anti-TNF reactivity, certolizumab pegol (CDP870), has also been approved for use [9].

The TNF inhibition group expanded with the additions of adalimumab (the most widely used biologic worldwide), certolizumab pegol and golimumab. Soon, alternative blockade was sought after. Anakinra is an IL-1 receptor antagonist, licensed for the treatment of RA in 2006. However it has been shown to be less potent than the TNF inhibitors in most patients [10,11] and as a result, is used less frequently now.

Abatacept, developed in 2007, is selective co-stimulation modulator causing the inhibition of T cells. It is a soluble fusion protein comprising CTLA-4 and the Fc portion of IgG1. It prevents CD28 from binding to its counter-receptor, CD80/CD86. The efficacy and safety of abatacept in RA has been analyzed in a 2009 meta-analysis. The meta-analysis included seven randomized trials with 2908 patients, comparing abatacept alone, in combination with synthetic or biologic DMARDs, with placebo alone or in combination with nonbiologic or biologic DMARDs [12]. Results were positive, with patients on abatacept being significantly more likely to achieve an ACR50 response at 1 year (ACR50 being a 50% improvement in tender or swollen joint counts, as well as 50% improvement in three of the other five criteria, including the patient's assessment of pain, global assessment of disease activity and physical function, the physician's assessment of physical function and an acute-phase reactant [13]). Physical function improvement, and reduced disease activity and pain were also significant. However, there was a significantly increased number of serious infections at 1 year, which was seen in another meta-analysis [14].

Table 1. Biological disease-modifying antirheumatic drugs.

Name	Target	Administration	Frequency	Mode of action
Abatacept	T-cell costimulation	iv. infusion, sc.	Week 0, 2 and 4, then monthly	Selective T-cell costimulation modulator
Adalimumab	TNF	sc.	Daily	Fully humanized antibody
Certolizumab pegol	TNF	sc.	Alternate weeks	Antibody: half synthetic and half human
Etanercept	TNF	sc.	Weekly/biweekly	Soluble receptor
Infliximab	TNF	iv. infusion	Week 0, 2 and 6, then 2 monthly	Chimeric monoclonal antibody
Golimumab	TNF	sc.	Monthly	Fully humanized antibody
Tocilizumab	IL-6	iv. infusion	Monthly	Antibody: half synthetic and half human
Rituximab	Anti-CD20	iv. infusion	Alternate weeks then 6 monthly	Chimeric monoclonal antibody
Anakinra	IL-1	sc.	Daily	Receptor antagonist

iv.: Intravenous; sc.: Subcutaneous.

A number of studies have also documented the efficacy of abatacept in certain important subsets of patients with RA [15–18]. In addition to clinical improvement, abatacept demonstrated inhibition of radiographic progression which was significant. Treatment of RA patients with abatacept has not been associated with an increased frequency of malignancy [19]. Efficacy and safety of both subcutaneous and intravenous preparations are comparable [20].

The fourth biologic, rituximab is a chimeric anti-CD20 monoclonal antibody causing B-cell depletion. It does this through one or more of the antibody-dependent mechanisms [21]: Fc receptor γ-mediated antibody-dependent cytotoxicity, antibody-dependent complement-mediated cell lysis, growth arrest and B-cell apoptosis. Rituximab is mostly used in the treatment of RA in patients who have failed TNF inhibitors. Seropositive patients with rheumatoid factor or antibodies to citrullinated peptides detectable positive, are more likely to respond to rituximab [22]. Finally, tocilizumab, an anti-IL-6 antibody, was developed in 2009. These five classes of different targets for biologic DMARDs have been shown to significantly decrease not only the inflammatory activity of RA, but also the radiographic progression.

What is the latest guidance on biological therapy for RA?

Leading recommendations for the treatment of RA come from the European League Against Rheumatism (EULAR) and ACR guidelines. National and international guidelines recommend prompt initiation of DMARD therapy once RA is diagnosed [23–26]. MTX is the recommended initial DMARD. EULAR recommends treating patients with RA with a combination of DMARDs plus glucocorticoid upon diagnosis [15,17]. ACR-recommended glucocorticoid or/and other DMARDs may be added to MTX for those patients with moderate/high disease activity or poor prognostic factors [16].

Several randomized controlled trials have compared combination DMARDs with/without glucocorticoid with MTX plus TNF inhibitors in DMARD-naive RA patients. ACR recommends the use of a TNF inhibitor (as monotherapy or in combination with MTX) as an immediate course of therapy for patients with early RA displaying high disease activity and poor prognostic factors [27].

In the SWEFOT trial, 258 patients with early RA who failed to achieve low disease activity despite MTX were randomized to additional treatment by either sulfasalazine and hydroxychloroquine or infliximab [28]. Low disease activity was more common with infliximab than sulfasalazine and hydroxychloroquine (39 vs 25%). However, a 'step-up' approach for combination therapy (i.e., therapy increased if response is inadequate) has been shown to be inferior to 'step-down' approach (i.e., initiated with combination therapy at the start) in the BeST trial in which 'step-down' combination therapy with either conventional DMARD combination plus glucocorticoid or MTX plus infliximab achieved greater reduction in DAS28, physical disability as measured by Health Assessment Questionnaire and radiographic joint damage than 'step-up' treatment by DMARDs [29]. The TEAR study also demonstrated similar DAS28 reduction comparing step-down combination conventional DMARDs (MTX plus sulfasalazine plus hydroxychloroquine) to MTX plus etanercept

(DAS28 score includes swollen and tender joints, acute phase reactant and patient global health score) [30]. Both were superior to step-up MTX monotherapy. However, after 2 years, radiographic damage was statistically significantly less in the group receiving MTX plus etanercept and the group receiving conventional DMARD combination (0.64 vs 1.69; p = 0.047).

In patients with severe active RA who are DMARD naive, there is no evidence to suggest the addition of a biologic agent is superior to the current standard of care using step-down DMARD combinations plus steroids, as recommended by NICE and EULAR. Whether patients with poor prognostic factors and severe active disease, as recommended by ACR, will benefit from early biologic treatment is unknown.

EULAR stipulated in 2013 to start biologic DMARDs with MTX (if not contraindicated), if synthetic DMARDs have failed to control disease (e.g., DAS >3.2). First-line biologic DMARDs recommended are TNF inhibitors, abatacept or tocilizumab. There are few head-to-head biologic trials but the AMPLE study, is a single-blind, randomized controlled trial that compared weekly subcutaneous abatacept 125 mg with 2-weekly subcutaneous adalimumab 40 mg in patients taking concomitant MTX [31]. It demonstrated similar clinical and radiographic efficacy. Rates of adverse events, serious adverse events, and infection were also similar. The study found the two agents to be similar in efficacy and adverse events, but with fewer discontinuations due to adverse events, injection site reactions and serious infections with abatacept.

Monotherapy

If synthetic DMARDs are not tolerated, adalimumab, etanercept, certolizumab and tocilizumab are monotherapy treatment options in Europe. In the USA but not in Europe, the license indication for abatacept in RA also includes monotherapy. The efficacy of abatacept monotherapy has not been compared with other biologic monotherapy. Combining MTX with either TNF inhibitors, abatacept or tocilizumab has been shown to be superior to MTX alone in reducing symptoms and signs as well as radiographic damage, in DMARD naïve patients [32]. As monotherapy, patients treated by etanercept [33,34] and adalimumab [35] had less radiographic joint damage but similar improvement in symptoms and signs when compared with MTX alone. Only tocilizumab monotherapy has been shown to be superior to MTX with more patients achieving ACR response and greater reduction in DAS28 in two randomized controlled trials [35].

Tocilizumab is the preferred biological DMARD, as monotherapy based on result of the ADACTA trial in which tocilizumab was shown to be superior to adalimumab [36]. ADACTA was a double-blind, double-dummy, placebo-controlled, randomized controlled trial comparing tocilizumab with adalimumab as monotherapy for RA [17]. The study of 326 patients with RA who were intolerant to MTX showed the reduction in DAS28 score at week 24 was significantly greater in the tocilizumab group (-3·3) than in the adalimumab group (-1.8; p < 0.0001). DAS28 remission, low disease activity, EULAR and ACR responses were all statistically significantly higher in the tocilizumab group. Clinical Disease Activity Index-based remission and low disease activity, which did not include any acute phase reactant (ESR or CRP) were also statistically significantly more frequent in the tocilizumab group.

Second-line biological DMARDs

Second-line biological treatment, to commence if failure to achieve target in a further 3–6 months, is to switch to second TNF inhibitors (plus synthetic DMARD) or a biologic with an alternative mode of action. If biologic treatment has failed, tofacitinib may be considered where approved [37].

Second-line biologic remains a contentious issue, with few research studies looking at whether the after-failed TNF therapy patients should be treated with yet another TNF inhibitor or change to medications with an alternative mode of action. Recent USA and Swedish data have suggested that the response rates of patients switching to a second or third TNF inhibitor are often lower than the response rates of patients to the first TNF inhibitor [38,39]. This was supported by Rendas-Baum *et al.*'s meta-analysis study, which concluded that for 'patients with prior exposure to TNF inhibitors, the likelihood of response to subsequent treatment with biologic agents declines with the increasing number of previous treatments with TNF-α inhibitors' [40]. At present, the decision of whether to treat with another TNF inhibitor or a biologic with an alternative mode of action is at the discretion of the clinician.

What are the latest developments in biological therapy for RA?

Anticytokines

TNF inhibitors

TNF inhibitors have been licensed for the treatment of RA for almost 15 years. One of these emerging developments are biosimilars. A biosimilar is a 'biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product' [41]. After the expiry of the patent of approved medications, any company can copy the medication and market the biosimilar. However, biosimilarity does not automatically suggest interchangeability.

Biosimilars must be demonstrated to be identical to the original product, based on results in clinical, analytical and animal studies. A Phase III trial compared infliximab to one of its biosimilars in patients previously treated with DMARDs with active RA, and achieved equivalent efficacy at week 30 and a comparable safety profile, and was well-tolerated in comparison to infliximab [42]. An infliximab biosimilar has been launched in central and eastern Europe in 2014 as patents expire. The price of biosimilars may be different, therefore its cost–effectiveness may alter the current guidance.

IL-6

IL-6 is secreted by T cells and macrophages to stimulate an immune response. It is a proinflammatory cytokine involved in immunologic responses during host infection, inflammatory disease, hematopoiesis and oncogenesis. RA patients have been found to have high IL-6 in synovial tissues, so it is implicated in upregulation of endothelial adhesion molecule expression, in osteoclast maturation and in bone erosion.

Tocilizumab is a humanized monoclonal antibody which targets IL-6 receptors. IL-6 blockade in human RA trials have shown beneficial effects on disease activity, anemia and bone erosion have been demonstrated upon. As a result, it was licensed for treatment of RA in Europe in 2009 [43]. Atlizumab is a recombinant humanized anti-IL-6 receptor being developed in Japan. Other anti-IL-6 monoclonal antibodies are also under development. Sarilimumab is in Phase III trials, currently being compared directly to etanercept in the RA-COMPARE study, whilst VX30 is in preclinical trials for RA.

IL-17

IL-17 is produced by effector T-helper cells and mast cells. IL-17 induces the production of cytokines including IL-6, TNF-α, TNF-β, G-CSF, GM-CSF, chemokines and prostaglandins.

IL-17 is thought to play an important role in joint degradation, demonstrated in the collagen-induced arthritis model in mice, IL-17A overexpression accelerated development of joint degradation and enhanced the severity of synovial inflammation and bone erosion [44]. A second study with human rheumatoid synovial and bone explants showed that IL-17A enhanced bone resorption and collagen degradation, and blocked collagen synthesis and bone formation [45].

Anti-IL-17 agent, secukinumab, unfortunately failed to meet its primary end point of 20% reduction in symptoms by ACR criteria (ACR20; a 20% improvement in tender or swollen joint counts, as well as 20% improvement in three of the other five criteria, including the patient's assessment of pain, global assessment of disease activity and physical function, the physician's assessment of physical function and an acute-phase reactant [13]) rate at week 16, in a Phase II trial reported in 2010 [46]. This raised doubts about IL-17 as a target.

Anti-IL-17, ixekizumab, indicated that it was better than placebo in Pase II trial. The study's primary end point, an ACR20 by week 12, showed that all ixekizumab doses produced higher response rates than placebo in the biologics-naive group [47]. Furthermore, it was effective in patients who had previously failed on TNF inhibitors. The safety profile was similar to other biological agents.

Brodalumab is a fully humanized anti-IL-17 that showed equivocal results. The primary end point was ACR50 at week 12, which was achieved by 10–16% of patients in the brodalumab groups compared with 13% of those in the placebo group. Mean changes from baseline in DAS28 also did not differ significantly between brodalumab and placebo groups [48].

Antilymphocytes therapies

B-cell modulators

Rituximab is licensed for the treatment of RA in patients who have failed TNF inhibitors. The patent for rituximab is due to expire in the next couple of years, which is why the emergence of new rituximab biosimilars is eagerly anticipated.

Ofatumumab is a monoclonal antibody which acts on B lymphocytes binding to the extracellular loops of the CD20 molecule causing potent complement-dependent cell lysis and antibody-dependent cell-mediated toxicity in cells that overexpress CD20. A combined Phase I/II study investigating the efficacy and safety of three doses of ofatumumab showed that it was clinically effective in patients with active RA [49]. In the USA, it is already approved for the treatment of refractory chronic lymphocytic leukemia.

Ocrelizumab is a recombinant human anti-CD20 monoclonal antibody, which was designed to optimize B-cell depletion. By modification of the Fc region when compared with rituximab, it enhances antibody-dependent cell-mediated cytotoxicity and decreases complement-dependent cytotoxicity [50]. Unfortunately, there were safety concerns due to the occurrence of serious and fatal infections in clinical trials so it has been withdrawn from development in RA.

Other B-cell targets

Because of the positive results seen with patients treated with rituximab in RA, it is hypothesized that other approaches that interfere with B-cell function or interfere with B-cell trafficking to the sites of inflammation may prove useful. B cell targets other than CD20 that have been suggested include the following.

Belimumab is a B-lymphocyte stimulator (anti-BLyS/BAFF) monoclonal antibody. It is currently approved for use in patients with systemic lupus erythematosus. Recently, it has been evaluated in RA patients with at least moderately active RA who have failed at one or more DMARD in a Phase II trial with 283 patients [51]. This found relatively modest benefits after 24 weeks of therapy compared with placebo; the only statistically significant difference was achieved with the lowest dose of belimumab. Its potential role in the treatment of RA as combination or monotherapy needs further study.

Atacicept is a recombinant fusion protein made up of a portion of the transmembrane activator, calcium modulator and an immunoglobulin chain (TACI-Ig). Atacicept targets molecules that promote B-cell survival including BLyS and APRIL, on the B-cell surface. A Phase I trial suggested that repeated dosing of atacicept significantly reduces immunoglobulin levels, including a 41–44% decrease in rheumatoid factor in the highest dose group [52]. However, two randomized Phase II studies with atacicept, with patients who had active RA and inadequate responses to MTX and to anti-TNF, failed to achieve their primary clinical efficacy end points, despite evidence of biologic effects [53,54].

Anti-CD3

Anti-CD3 monoclonal antibody binds T cells. The first to be approved was muronomab in 1986 and has been used to treat transplant rejection through immunosuppression. Newer anti-CD3 preparations include otelixzumab and teplizumab, both have been shown to preserve residual β-cell function in patients with recent onset Type 1 diabetes. Visilizumab and foralumab are being tested for their use in inflammatory bowel disease. Results in the collagen-induced arthritis model show that anti-CD3 action may have important therapeutic potential for rheumatoid arthritis with the ability to generate $CD8^+$ Tregs and increase the relative numbers of $CD4^+$ Tregs [55].

However, these CD3-directed therapies have observed intolerable adverse events such as evoking cytokine-related reactions and EBV reactivation, in the Phase I/II pilot trials. The dose of anti-CD3 antibodies was reduced in the Phase II/III confirmatory trials but regrettably low doses of monotherapy are ineffective. Combining anti-CD3 with other drugs may be the most effective way to reduce toxicity but also allow therapeutic benefit. Combination therapy of anti-CD3 and TNF inhibitors efficiently depletes pathogenic T cells from the draining lymph nodes, reducing the numbers of T cells in the joints and resulting in long-lasting inhibition of established collagen-induced arthritis [56]. New developments into identifying the appropriate combination of immunomodulation with anti-CD3, could result in synergistic effects in the clinical setting. Administering an oral form of anti-CD3 means that there is no systemic drug exposure and thus no generalized immunosuppression associated with EBV reactivation, and no side effects related to cytokine release [57]. It would therefore be ideal for chronic treatment.

Anti-CD28

CD28 is a potent costimulator of T cells. CD28 augments cytotoxicity of CD3-activated T cells, IL-2 and IL-2 receptor expression. Preclinical models showed that the stimulation of CD28 with TGN1412 (an anti-CD28) activated and expanded type 2 helper T cells, resulting in transient lymphocytosis with no detectable toxic or proinflammatory effects [58–60]. In animal models, both prophylactic and therapeutic administration of a CD28 superagonist prevented or at least mitigated clinical symptoms and induced remission. However, a Phase I clinical trial of six patients with TGN1412 resulted in multiorgan failure of all subjects [61] and severe unexpected lymphopenia. Therefore, development of anti-CD28 has been stopped.

Oral agents

JAK inhibitor

Tofacitinib is an orally administered JAK inhibitor that decreases a number of cytokine signaling and growth factor receptors. It preferentially inhibits JAK1 and JAK3, but it is active on all of the JAK isoforms. The JAKs are cytoplasmic protein tyrosine kinases that are essential for signal transduction from the plasma membrane receptors for IL-2, -4, -7, -9, -15 and -21, to the nucleus. Tofacitinib interrupts this important signal transduction of cytokines, which add to the aberrant immune response in RA.

Tofacitinib monotherapy results showed significantly more reduction in signs and symptoms of active RA after 3 months of treatment, compared with placebo (ACR20 of 60 vs 27%) [62] in a randomized trial of 611 patients with an inadequate response to one or more synthetic or biologic DMARD (usually MTX). It has also shown benefit in combination with MTX in patients who have not had an adequate response to MTX as a monotherapy, and was comparably effective to an anti-TNF in this setting [63]. Tofacitinib reduced disease activity in RA in a series of Phase II/III trials, including patients with inadequate responses to MTX, other traditional synthetic DMARDs and TNF inhibitors [64–68]. The potent inhibition of JAK signaling can lead to some important side effects such as severe infections, including opportunistic infections. However, infection rates were comparable to those seen with other biologic DMARDs [69].

Research into more oral alternatives continues. These include promising investigation into the testing of secukinumab, an anti-IL-17, baricitinib, masitinib, and sirukumab – an anti-IL-6. The results are not available yet and would not be expected to be ready for appraisal until the end of 2014.

Syk inhibition

Fostamatinib disodium, a small molecule orally administered inhibitor of Syk, has shown benefit in three Phase II clinical trials for patients with active RA [70–72]. Syk is an intracellular cytoplasmic tyrosine kinase that mediates immune receptor signaling in macrophages, neutrophils, mast cells and B cells; it is important for cytokine and metalloproteinase production induced by TNF in fibroblast-like synoviocytes in patients with RA. Some research has suggested that this oral agent may work in patients who do not respond to TNF inhibition.

Evidence with fostaminib is conflicting. In a Phase II trial, 457 active RA patients despite treatment with concurrent MTX, were treated with fostamatinib versus placebo. Patients receiving fostamatinib showed significant benefit after 6 months and the benefits are similar to those observed with parenterally administered biologic agents. By contrast, another study with patients who had previously failed TNF inhibitors did not show benefit with this agent; this could be due to trial design or true biologic issues. As expected with immunomodulation, Phase II trials confirm preliminary reports of infections, including serious infections, appear increased in the first 6 months of therapy and that liver test abnormalities and neutropenia can be seen [73]. Diarrhea and hypertension are also more common with fostamatinib compared with tofacitinib. The recent Phase III OSKIRA-3 trial in June 2013, looking at patients who did not respond to MTX and then one TNF inhibitor, demonstrated that fostamatinib in combination with MTX, showed improvements in ACR20 at 24 weeks ($p = 0.004$; NCT01197755) [74]. However, as the findings were not deemed as being as promising as results seen in earlier trials, fostamatinib development has stopped.

Conclusion

Biologics have transformed the management of RA; however, they are expensive. Consequently, reimbursement and funding authorities limit their usage in clinical practice. With increasing number of biologic agents becoming available, competition has led to slight reduction in price in some countries; this is likely to accelerate especially with the small molecule inhibitors such as the JAK inhibitors. In some countries, reduction in dose is recommended in patients who are in remission. Clinical studies have shown that while some patients remained in low disease activity, many patients flared. These studies have failed to identify predictor of outcome. Furthermore, one theoretical risk of stopping and re-starting biologic therapy is that it may increase the risk of immunogenicity that could impact on the efficacy on restarting treatment. This will need to be examined in future clinical trials.

Unlike small molecules, proteins are large and complex, making generic biologics is impossible. However, it is feasible to create biosimilars which are similar in molecular composition. Biosimilars of recombinant cytokines and hormones such as somatropin, erythopoetin and filgrastim are already available. They are usual cheaper than their parent biologics with discount ranging from 5 to 82% [75]. Consequently, the development of biosimilars may reduce cost and widen access to treatment in the future. New targets being explored include cytokine such as IL-17, B-cell cytokines such as BAFF and intracellular signaling pathways. This growing market of alternative agents may finally kick start the competitive cost market and begin to make biological agents more available. A competitive market will impact positively on healthcare as more options available will enable clinicians to better target disease and optimize healthcare.

Future perspective

Unlike small molecules, proteins are large and complex, making generic biologics is impossible. However, it is feasible to create biosimilars which are similar in molecular composition. Biosimilars of recombinant cytokines and hormones such as somatropin, erythopoetin and filgrastim are already available. They are usual cheaper than their parent biologics with discount ranging from 5 to 82%. Consequently, the development of biosimilars may reduce cost and widen access to treatment in the future. New targets being explored include cytokine such as IL-17, B-cell cytokines such as BAFF and intracellular signaling pathways. This growing market of alternative agents may finally kick start the competitive cost market and begin to make biological agents more available. A competitive market will impact positively on healthcare as more options available will enable clinicians to better target disease and optimize healthcare.

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Executive summary

What is the latest guidance on biological therapy for rheumatoid arthritis?

- International guidelines recommend prompt initiation of disease-modifying antirheumatic drug (DMARD) therapy once rheumatoid arthritis (RA) is diagnosed. Methotrexate (MTX) is the recommended initial DMARD.
- The European League Against Rheumatism stipulated in 2013 to start biologic DMARDs with MTX if synthetic DMARDs have failed to control disease.

Monotherapy

- If synthetic DMARDs are not tolerated, adalimumab, etanercept, certolizumab and tocilizumab are monotherapy treatment options in Europe. Only tocilizumab monotherapy has been shown to be superior to MTX.

Second-line biological DMARDs

- Second-line biological treatment is to switch to second TNF inhibitors or a biologic with an alternative mode of action.

Latest developments in biological therapy for RA: anticytokines

- TNF inhibitors biosimilars
  - An infliximab biosimilar has been launched in central and eastern Europe in 2014. The price of biosimilars may be different therefore its cost–effectiveness may alter the current guidance.
- IL-6
  - Atlizumab is a recombinant humanized anti-IL-6 receptor. Sarilimumab is in Phase III trials, currently being compared directly to etanercept in the RA-COMPARE study, whilst VX30 is in preclinical trials for RA.
- IL-17
  - Anti-IL-17 agent secukinumab unfortunately failed to meet its primary end point of ACR20 at week 16.
  - Anti-IL-17 ixekizumab, showed that all doses produced higher response rates than placebo in the biologics-naive group.
  - Brodalumab is a fully humanized anti-IL-17 that showed equivocal results.

Latest developments in biological therapy for RA: antilymphocyte therapies

- B-cell modulators
  - The patent for rituximab is due to expire in the next couple of years so biosimilars are eagerly anticipated.
  - Ofatumumab is a monoclonal antibody, which acts on B lymphocytes binding to the CD20, showed that it was clinically effective in patients with active RA.
  - Ocrelizumab is a recombinant human anti-CD20 monoclonal antibody designed to optimize B-cell depletion; it was withdrawn due to safety concerns.
- Other B-cell targets
  - Belimumab is a B-lymphocyte stimulator (anti-BLyS/BAFF) monoclonal antibody. A study looking at moderately active RA patients who have failed one or more DMARD, found relatively modest benefit compared with placebo.
  - Atacicept targets molecules that promote B-cell survival including BLyS and APRIL. Two randomized Phase II with patients who had active RA and inadequate responses to MTX and to anti-TNF, failed to achieve their primary clinical efficacy end points.
- Anti-CD3
  - Anti-CD3 monoclonal antibody binds T cells. CD3-directed therapies have observed intolerable adverse events so the dose was reduced but low doses are ineffective.
- Anti-CD28
  - CD28 is a potent costimulator of T cells. A Phase I clinical trial of six patients with TGN1412 resulted in multiorgan failure of all subjects and severe unexpected lymphopenia.

Oral agents

- JAK inhibitor
  - Tofacitinib is an orally administered JAK inhibitor. Monotherapy results showed significantly more reduction in signs and symptoms of active RA after of treatment compared to placebo. More oral alternatives include secukinumab, an anti-IL-17, baricitinib, masitinib, and sirukumab, an anti-IL-6. The results are not available yet.
- Syk inhibition
  - Fostamatinib disodium, a small molecule orally administered inhibitor of Syk, was not deemed as being as promising as results seen in earlier trials so development has stopped.

Executive summary (cont.)

Conclusion

- Increasing number of biologic agents and competition has led to slight reduction in price in some countries.
- Biosimilars are usual cheaper than their parent biologics with discount ranging from 5 to 82%.
- New targets being explored include cytokine such as IL-17, B-cell cytokines such as BAFF and intracellular signaling pathways.
- A competitive market will enable clinicians to better target disease and optimize healthcare.

References

1 McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N. Engl. J. Med.* 365, 2205–2219(2011).

2 Solomon DH, Karlson EW, Rimm EB *et al.* Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 107, 1303–1307 (2003).

3 Holmqvist ME, Wedren S, Jacobsson LT *et al.* Rapid increase in myocardial infarction risk following diagnosis of rheumatoid arthritis amongst patients diagnosed between 1995 and 2006. *J. Intern. Med.* 268, 578–585(2010).

4 van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann. Rheum. Dis.* 73(5), 861–870 (2013).

5 Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 43, 906–914(2004).

6 Emery P, Kvien TK, Combe B *et al.* Combination etanercept and methotrexate provides better disease control in very early (≤4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study. *Ann. Rheum. Dis.* 71, 989–992(2012).

7 Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* 2(8657), 244–247(1989).

8 Tak PP, Taylor PC, Breedveld FC *et al.* Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. *Arthritis Rheum.* 39(7), 1077 (1996).

9 Ramiro S, van Tubergen AM, Landewé RB. RAPID and FAST4WARD trials: certolizumab pegol for rheumatoid arthritis. *Expert Rev. Clin. Immunol.* 6(5), 713–720(2010).

10 Callhoff J, Weiß A, Zink A, Listing J. Impact of biologic therapy on functional status in patients with rheumatoid arthritis: a meta-analysis. *Rheumatology (Oxford)* 52(12), 2127–2135 (2013).

11 Mertens M, Singh JA. Anakinra for rheumatoid arthritis. *Cochrane Database Syst. Rev.* 1, CD005121 (2009).

12 Saag KG, Teng GG, Patkar NM *et al.* American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 59, 762–784 (2008).

13 Felson DT, LaValley MP. The ACR20 and defining a threshold for response in rheumatic diseases: too much of a good thing. *Arthritis Res. Ther.* 16, 101 (2014).

14 Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. *J. Rheumatol.* 37(2), 234 (2010).

15 Kremer JM, Westhovens R, Leon M *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N. Engl. J. Med.* 349(20), 1907 (2003).

16 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 144(12), 865 (2006).

17 Kremer JM, Genant HK, Moreland LW *et al.* Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum.* 58(4), 953 (2008).

18 Westhovens R, Robles M, Ximenes AC *et al.* Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann. Rheum. Dis.* 68(12), 1870 (2009).

19 Simon TA, Smitten AL, Franklin J *et al.* Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. *Ann. Rheum. Dis.* 68(12), 1819 (2009).

20 Genovese MC, Covarrubias A, Leon G *et al.* Subcutaneous abatacept versus intravenous abatacept: a Phase IIIbnoninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum.* 63(10), 2854 (2011).

21 Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. *Curr. Dir. Autoimmun.* 8, 140 (2005).

22 Isaacs JD, Cohen SB, Emery P *et al.* Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. *Ann. Rheum. Dis.* 72(3), 329–336 (2013).

23 National Institute for Health and Clinical Excellence. Clinical Guideline 79 – Rheumatoid arthritis 2009. www.nice.org.uk/guidance/CG79

24 Singh JA, Furst DE, Bharat A *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res. (Hoboken)* 64(5), 625–639(2012).

25 Smolen JS, Landewé R, Breedveld FC *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann. Rheum. Dis.* 69(6), 964–975 (2010).

26 Kennedy T, McCabe C, Struthers G *et al.* British Society for Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). BSR guidelines on standards of care for persons with rheumatoid arthritis. *Rheumatology (Oxford)* 44(4), 553–556 (2005).

27 Singh JA, Furst DE, Bharat A *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res.* 64(5), 625–639 (2012).

28 vanVollenhoven RF, Ernestam S, Geborek P *et al.* Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* 374(9688), 459–466 (2009).

29 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 52(11), 3381–3390 (2005).

30 Moreland LW, O'Dell JR, Paulus HE *et al.* TEAR Investigators. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis trial. *Arthritis Rheum.* 64(9), 2824–2835 (2012).

31 Weinblatt ME, Schiff M, Valente R *et al.* Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a Phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum.* 65(1), 28–38 (2013).

32 Singh JA, Christensen R, Wells GA *et al.* Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database Syst. Rev.* 4, CD007848 (2009).

33 Bathon JM, Martin RW, Fleischmann RM *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N. Engl. J. Med.* 343(22), 1586–1593(2000).

34 Klareskog L, van der Heijde D, de Jager JP *et al.* TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363(9410), 675–681 (2004).

35 Breedveld FC, Weisman MH, Kavanaugh AF *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 54(1), 26–37 (2006).

36 Burmester G, Rigby W, van Vollenhoven R *et al.* Tocilizumab in combination and monotherapy versus methotrexate (MTX) in MTX-naive patients with early rheumatoid arthritis: clinical and radiographic outcomes from a randomised, placebo-controlled trial. *Ann. Rheum. Dis.* 72(Suppl.), OP004 (2013).

37 Gabay C, Emery P, van Vollenhoven R *et al.* ADACTA Study Investigators. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled Phase 4 trial. *Lancet* 381(9877), 1541–1550 (2013).

38 Smolen J, Landewé R, Breedveld FC *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* 73(3), 492–509 (2014).

39 Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor α agent to a second anti-tumor necrosis factor α agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum.* 56, 13–20 (2007).

40 Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 47, 507–513 (2008).

41 Rendas-Baum R, Wallenstein GV, Koncz T *et al.* Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor-α inhibitors. *Arthritis Res. Ther.* 13(1), R25 (2011).

42 WHO definition. http://gabionline.net/Biosimilars/General/WHO-definitions-of-biosimilars

43 Yoo DH, Hrycaj P, Miranda P. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann. Rheum. Dis.* 72(10), 1613–1620 (2013).

44 Oldfield V, Dhillon S, Plosker GL. Tocilizumab: a review of its use in the management of rheumatoid arthritis. *Drugs* 69(5), 609–632 (2009).

45 Lubberts E, Joosten L, Oppers B *et al.* IL-1–independent role of IL-17 in synovial inflammation and joint destruction during collagen-induced arthritis. *J. Immunol.* 167, 1004–1013 (2001).

46 Chabaud M, Lubberts E, Joosten L, van den Berg W, Miossec P. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. *Arthritis Res.* 3, 168–177 (2001).

47 Genovese M, Greenwald M, Cho CS *et al.* A Phase 2 study of multiple subcutaneous doses of LY2439821, an anti-IL17 monoclonal antibody, in patient with rheumatoid arthritis in tow populations: naïve to biologic therapy or inadequate responders to tumour necrosis factor alpha inhibitors. *Ann. Rheum. Dis.* 71(Suppl. 3), 59 (2012).

48 Genovese MC, Greenwald M, Cho CS *et al.* Phase 2 randomized study of subcutaneous ixekizumab, an anti-IL-17 monoclonal antibody, in biologic-naive or TNF-IR patients with rheumatoid arthritis. *Arthritis Rheum.* doi:10.1002/art.38617 (2014) (Epub ahead of print).

49 Pavelka K, Chon Y, Newmark R, Erondu N, Lin S. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Rheum.* 64(10), S362 (2012).

50 Østergaard M, Baslund B, Rigby W *et al.* Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, Phase I/II study. *Arthritis Rheum.* 62(8), 2227 (2010).

51 Genovese MC, Kaine JL, Lowenstein MB *et al.* Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a Phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum.* 58(9), 2652 (2008).

52 Stohl W, Merrill JT, McKay, *et al.* Efficacy and safety of belimumab in patients with rheumatoid arthritis: a Phase II, ramdomised, double-blind, placebo-controlled, dose-ranging Study. *J. Rheumatol.* 40(5), 579–589 (2013).

53 Tak PP, Thurlings RM, Rossier C *et al.* Atacicept in patients with rheumatoid arthritis: results of a multicenter, Phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. *Arthritis Rheum.* 58(1), 61 (2008).

54 vanVollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a Phase II, randomized, placebo-controlled trial. *Arthritis Rheum.* 63(7), 1782 (2011).

55 Genovese MC, Kinnman N, de La Bourdonnaye G, Pena Rossi C, Tak PP. Atacicept in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor antagonist therapy: results of a Phase II, randomized, placebo-controlled, dose-finding trial. *Arthritis Rheum.* 63(7), 1793 (2011).

56 Notley CA, McCann FE, Inglis JJ, Williams RO. Anti-CD3 therapy expands the numbers of CD4+ and CD8+ Treg cells and induces sustained amelioration of collagen-induced arthritis. *Arthritis Rheum.* 62(1), 171–178 (2010).

57 Dépis F, Hatterer E, Lamacchia C *et al.* Long-term amelioration of established collagen-induced arthritis achieved with short-term therapy combining anti-CD3 and anti–tumor necrosis factor treatments. *Arthritis Rheum.* 64(10), 3189–3198 (2012).

58 da Cunha AP, Weiner HL. Induction of immunological tolerance by oral anti-CD3. *Clin. Dev. Immunol.* 2012, 425021 (2012).

59 Beyersdorf N, Gaupp S, Balbach K *et al.* Selective targeting of regulatory T cells with CD28 superagonists allows effective therapy of experimental autoimmune encephalomyelitis. *J. Exp. Med.* 202(3), 445–455 (2005).

60 Luhder F, Huang Y, Dennehy KM *et al.* Topological requirements and signaling properties of T cell-activating, anti-CD28 antibody superagonists. *J. Exp. Med.* 197, 955–966 (2003).

61 Rodriguez-Palmero M, Hara T, Thumbs A, Hunig T. Triggering of T cell proliferation through CD28 induces GATA-3 and promotes T helper type 2 differentiation in vitro and in vivo. *Eur. J. Immunol.* 29, 3914–3924 (1999).

62 Suntharalingam G, Perry M, Ward S *et al.* Cytokine storm in a Phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N. Engl. J. Med.* 355, 1018–1028 (2006).

63 Fleischmann R, Kremer J, Cush J *et al.* Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N. Engl. J. Med.* 367(6), 495–507 (2012).

64 van der Heijde D, Tanaka Y, Fleischmann R *et al.* Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month Phase III randomized radiographic study. *Arthritis Rheum.* 65(3), 559–570 (2013).

65 Fleischmann R, Kremer J, Cush J *et al.* Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N. Engl. J. Med.* 367(6), 495–507 (2012).

66 Kremer JM, Bloom BJ, Breedveld FC *et al.* The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled Phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum.* 60(7), 1895 (2009).

67 Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res. (Hoboken)* 63(8), 1150 (2011).

68 Fleischmann R, Cutolo M, Genovese MC *et al.* Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum.* 64(3), 617–629 (2012).

69 Fleischmann R. Novel small-molecular therapeutics for rheumatoid arthritis. *Curr. Opin. Rheumatol.* 24(3), 335–341 (2012).

70 van Vollenhoven RF, Fleischmann R, Cohen S *et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N. Engl. J. Med.* 367(6), 508–519 (2012).

71 Weinblatt ME, Kavanaugh A, Burgos-Vargas R *et al.* Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial. *Arthritis Rheum.* 58(11), 3309 (2008).

72 Genovese MC, Kavanaugh A, Weinblatt ME *et al.* An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, Phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. *Arthritis Rheum.* 63(2), 337–345 (2011).

73 Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N. Engl. J. Med.* 363(14), 1303–1312 (2010).

74 Evaluation of effectiveness of two dosing regimens of fostamatinib compared to placebo in patients with rheumatoid arthritis (RA) who are taking methotrexate and have had inadequate response to single TNF-alpha antagonist (OSKIRA - 3). http://clinicaltrials.gov/show/NCT01197755

75 Rovira J, Espín J, García L, Olry de Labry A. The impact of biosimilars' entry in the EU market (2011). http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en. pdf