Chapter 11

NEW BIOLOGIC AGENTS AND BIOSIMILARS DEVELOPED FOR RHEUMATOID ARTHRITIS

Laura Attipoe, MBBS[1], Katie Bechman, MBBS[2] and Coziana Ciurtin, MBBS MSc PhD[1,2,3,*]

[1]Department of Rheumatology, University College London Hospital NHS Foundation Trust, London, UK
[2]Department of Rheumatology, Hammersmith Hospital, London, UK
[3]Centre for Rheumatology, Department of Medicine, University College London, London, UK

ABSTRACT

The pathogenesis of rheumatoid arthritis (RA) is characterised by interactions between several types of immune cells, which are associated with the release of multiple inflammatory cytokines. Recently, numerous biologic treatments targeting classes of immune cells, cytokines or intracellular pathways of pro-inflammatory signals have been developed. Some of them are currently under research as potential therapeutic options for RA patients. This chapter reviews the available evidence regarding the safety and efficacy of new biologic agents targeting B cells, proinflammatory interleukins (IL), T helper 17 (Th17) pathway and intracellular enzymes. This chapter reviews the most relevant randomised

[*]Corresponding author: Dr. Coziana Ciurtin, Department of Rheumatology, University College London Hospital NHS Foundation Trust, 250 Euston Road, London, NW1 2PG, email: c.ciurtin@ucl.ac.uk.

controlled trials (RCTs) which have proven the efficacy of different biologic agents and small molecule inhibitors in controlling the inflammation associated with RA. The management of RA remains a dynamic and evolving field. The development of less expensive 'biosimilar' drugs, analogous to existing licensed biologic therapies, is an emerging area of research that deserves particular attention.

Keywords: rheumatoid arthritis, new biologic therapies, ofatumumab, ocrelizumab, veltuzumab, tregalizumab, alemtuzumab, mavrilimumab, ustekinumab, secukinumab, apremilast, biosimilars, efficacy, safety, cost-effectiveness

INTRODUCTION

Following the therapeutic success of biologic agents targeting B cell depletion and IL6 inhibition, the research in the field of rheumatology led to the discovery of other biologic agents with similar targets, but different mechanisms of action, properties and dose regimens. In addition, new biologic pathways, such as the Th17/IL17 pro-inflammatory pathway and blockage of intracellular enzyme activation or other pro-inflammatory interleukins were tested in patients with RA, and showed promising results. As the cost-effectiveness of biologic agents is a limiting factor for their widespread use, additional interest was directed into developing biosimilars of the already licensed biologic treatments for RA.

B CELL DEPLETION THERAPY (ANTI CD-20)

Ofatumumab

Ofatumumab is a fully human anti-CD20 monoclonal antibody (mAb). A joint phase I/II study investigated the safety and efficacy of ofatumumab in active RA patients who had not had an adequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). A proportion of 70% of patients had a moderate or good European League against Rheumatism (EULAR) response and there were no significant safety concerns [1].

A phase III RCT in biologic-naive patients looked at the effect of ofatumumab, 700mg intravenously (IV) given two weeks apart, in combination with methotrexate (MTX). At week 24, ofatumumab achieved statistically

significant American College of Rheumatology (ACR) 20 responses of 50% compared to a 27% placebo response (P<0.001). The most common adverse events (AEs) were rash and urticaria, especially on the first infusion day. First dose infusion related reactions were significantly higher at 68% vs. 6% placebo; however, this rate of AEs for the active drug was markedly reduced to <1% with the second infusion. There were no episodes of immunogenicity [2]. Ofatumumab has a unique binding site (epitope) on the human CD20 molecule, compared to other antiCD20 mAbs including rituximab. The membrane proximity of this epitope likely accounts for the greater efficacy of complement activation and B cell depletion observed with ofatumumab [3].

Other phase III trials were prematurely terminated as the sponsor wanted to refocus clinical development on subcutaneous (SC) preparations rather than IV delivery, with the aim of achieving a slower rate of absorption and B cell depletion with subsequent fewer infusion reactions [4-5]. A phase I/II trial of SC ofatumumab has shown efficacy at low doses with mild to moderate infusion reactions with higher doses [6].

Ocrelizumab [Table 1]

Ocrelizumab is a humanized mAb that selectively targets CD20 positive B cells. Like rituximab, it is also given as 2 infusions 2 weeks apart.

Clinical trials of ocrelizumab, in combination with MTX, in patients with an inadequate response to MTX monotherapy [7]; and of ocrelizumab, in combination with either MTX or leflunomide, in patients with an inadequate response to tumour necrosis factor (TNF) blockers [8] were completed. Both trials showed statistically significant (P<0.0001) improvement in all ACR responses, disease activity score 28 (DAS28) remission, and clinically meaningful improvement in health assessment questionnaire disability index (HAQ-DI) scores, compared to placebo.

In inadequate responders to TNF inhibitors, 200mg dosing vs. 500mg dosing was associated with ACR20 responses at week 24 of 42.2% and 47.9% respectively, in comparison to a placebo response of 22%. All ACR responses were sustained at week 48. The 500mg dosing regimen showed superiority with a statistically significant reduction in radiographic progression of 61% (P=0.0017). AEs were of similar frequency between all groups, serious infections were more common in the ocrelizumab group. The most common AEs were infusion related reactions with 19.1% in the 200mg group and 23.8% in the 500mg group.

A Japanese study of ocrelizumab and MTX combination therapy in patients who had failed MTX monotherapy was terminated early due to an increased incidence of serious infection, including *Pneumocystis jiroveci*, in the ocrelizumab group [9].

As a consequence of the above studies not showing significant benefit over existing biologics, including rituximab, a decision was made not to further investigate ocrelizumab as a treatment for RA [7]. Further studies continue to see if ocrelizumab may be of benefit in multiple sclerosis and other immune mediated conditions.

Table 1. Anti-CD20

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Genovese et al. 2015 (SCRIPT)	48 week RCT of ocrelizumab IV with MTX or leflunomide Group 1: ocrelizumab 200mg x2 Group 2: ocrelizumab 500mg x2 Group 3: placebo	Week 24 ACR20, change from baseline in HAQ-DI scores Group 1: 42.2%, 52.3% Group 2: 47.9%, 58.5% Group 3: 22%, 32.9%

Legend: ACR 20 – American College of Rheumatology 20% response criteria; HAQ-DI – health assessment questionnaire – damage index; IV – intravenously; N – number of patients; RCT – randomised controlled trial.

Veltuzumab

Veltuzumab is a humanized anti-CD20 mAb. A phase II RCT of veltuzumab, in patients who had failed either MTX or MTX in combination with TNF inhibitors, was terminated for study re-design with no safety issues having been identified. No results have been posted [10]. Delays in production leading to termination of licensing agreements have been reported in the press.

ANTI-CD4

Tregalizumab

CD4+CD25+ regulatory T cells are vital for maintaining autoimmune tolerance. The humanized CD4-specific mAb, tregalizumab, activates T regulatory cells by binding to CD4 and activating downstream pathways [11].

A 6 week phase I/IIa dose escalation trial of tregalizumab monotherapy in RA patients with an inadequate response to DMARDs showed a meaningful improvement in ACR20/50/70 responses [12]. Numerical results are not available. However, a subsequent 24 week phase IIb study failed to reach its primary endpoint and the trial was terminated [13].

ANTI-CD52

Alemtuzumab

Alemtuzumab (CAMPATH-1H) is an anti-lymphocyte humanised immunoglobulin (Ig) G1 mAb, directed against the surface antigen CD52, which is present on all lymphocytes and some monocytes.

A phase I trial of alemtuzumab in RA was terminated early due to concerns over toxicity, primarily severe adverse events (SAEs) [14]. There was one death due to opportunistic infection and one episode of haemolytic uraemic syndrome. Efficacy was assessed by modified Paulus criteria. A 50% Paulus response required four out of six of the following: > 50% improvement in tender joint score, swollen joint score, early morning stiffness, erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) and/or >2-point improvement in patient global assessment or physician global assessment. Three out of five patients with a disease duration of < 3 years achieved a 50% Paulus response for 6 months. Only 4 out of 30 with a disease duration of > 3 years achieved this same end point (P=0.07) [15].

RA patients at 12 year follow up continued to have long-term alterations in lymphocyte subsets compared to age-matched disease controls. The clinical significance of this remains uncertain however vaccine responses were within normal limits [16]. Due to a lack of efficacy over already available licensed biologics, alemtuzumab was not developed further as a treatment for RA.

INTERFERON BETA 1α

Interferon beta 1α is a cytokine shown to reduce synovial inflammation by inhibition of TNF and IL1β secretion, whilst also increasing production of the IL1 receptor antagonist [17-18]. A 6 month phase II trial of three times weekly SC interferon beta-1α injections, in combination with MTX, did not show any clinical or radiological benefit [19].

ANTI-GRANULOCYTE COLONY MACROPHAGE STIMULATING FACTOR (GM-CSF) [TABLE 2]

Mavrilimumab is a fully human mAb targeting the alpha subunit of the GM-CSF receptor. GM-CSF is thought to modulate the pathogenesis of RA through the activation and differentiation of neutrophils and macrophages.

A 12 week, phase II study RCT investigating mavrilimumab and MTX combination therapy in patients with an inadequate response to MTX showed efficacy of all mavrilimumab doses, with success in achieving the primary end point of ≥1.2 decrease in DAS28-CRP (41-66.7% versus placebo response of 34.7%. The highest mavrilimumab dose, 100mg SC every fortnight, also significantly improved DAS28 scores, all ACR categories and HAQ-DI.

Table 2. Anti-GMCSF

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Burmester et al. 2013	12-week, phase II randomised, double blind, placebo-controlled trial. Group 1: 10mg mavrilimumab SC every fortnight (N = 39) Group 2: 30mg mavrilimumab SC every fortnight (N = 41) Group 3: 50mg mavrilimumab SC every fortnight (N = 39) Group 4: 100mg mavrilimumab SC every fortnight (N = 39) Group 5: Placebo (N = 75)	≥1.2 decrease in DAS28-CRP at week 12: Group 1: 41% Group 2: 61% Group 3: 53.8% Group 4: 66.7% Group 5: 34.7%

Legend: DAS28-CRP- disease activity score assessing 28 joints and the C reactive protein; N – number of patients; SC – subcutaneously.

AEs were mild to moderate with the most common being a reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) >20% from baseline, nasopharyngitis and upper respiratory tract infections [20]. Similar findings were found in a Japanese cohort of patients [21]. Results are currently pending from a trial of mavrilimumab versus golimumab [22].

INTERLEUKIN 12/23 [TABLE 3]

Ustekinumab (Stelara™, Janssen) and Guselkumab

Ustekinumab acts against the p40 subunit of both IL12 and IL23, whereas guselkumab is specific to the p19 subunit of IL23 [23].

A phase II RCT evaluating the anti IL12/23 agents ustekinumab and guselkumab in patients with active RA, despite concomitant MTX therapy, has not shown any statistically significant efficacy [24]. The AE rate was similar between active and placebo groups.

Table 3. Anti IL12/23

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Smolen et al. 2015	A 28-week phase II, randomized, double blind, placebo-controlled, parallel-group trial. Group 1: 90mg ustekinumab 8 weekly (N = 55) Group 2: 90mg ustekinumab 12 weekly (N = 55) Group 3: 200mg guselkumab 8 weekly (N = 54) Group 4: 50mg guselkumab 8 weekly (N = 55) Group 5: Placebo (N = 55)	ACR20 at week 28: Group 1: 52.7% Group 2: 54.5% Group 3: 44.4% Group 4: 38.2% Group 5: 40% Not statistically significant

Legend: ACR 20 – American College of Rheumatology 20% response criteria; N – number of patients.

INTERLEUKIN 15

IL15 is produced in RA synovium. Treatments given to block IL15 have suppressed IL15 dependent T cell lines and induced apoptosis. CD3+ T cell subsets expressing CD69 have also been reduced. CD69 is a marker of T cell activation, thereby implying that IL15 is partially involved in T cell activation in the synovium [25].

HuMax-IL15 is a high-affinity, fully human IgG1 anti–IL15 mAb generated in human Ig–transgenic mice.

A phase I-II, 12 week, proof of concept study of HuMax-IL15 SC monotherapy in 30 patients showed an ACR20 response in 63% [25]. Side effect profile was similar to other biologics, with reports of mild injection site reactions, transient pyrexia, upper respiratory tract infections and influenza like symptoms. No further studies have been published.

INTERLEUKIN 17 [TABLE 4]

The interleukin-17 (IL17)/IL17 receptor (IL17R) family have an important role in the pathogenesis of RA. Mouse models for inflammatory arthritis demonstrated that blocking endogenous IL17A suppresses arthritis development and joint damage [26]–[28]. Agents that directly target IL17A or its receptor are currently available, and have been tested in several autoimmune rheumatic diseases.

Table 4. Anti IL17

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Hueber et al. 2010	16 week, randomised, placebo controlled trial. Group 1: secukinumab 10mg/kg (N = 26) Group 2: placebo (N = 26)	ACR20 Results Group 1: 54% (P=0.8) Group 2: 31%
Genovese et al. 2010	52 week phase II randomised, double blind, and placebo-controlled, dose-finding trial. Group 1: 300mg SC secukinumab (N = 41) Group 2: 150mg SC secukinumab (N = 43) Group 3: 75mg SC secukinumab (N = 49) Group 4: 25mg SC secukinumab (N = 54) Group 5: Placebo (N = 50)	ACR20 Results: Group 1: 53.7% Group 2: 46.5% Group 3: 46.9% Group 4: 34% Group 5: 36% Not statistically significant

Genovese et al. 2010	16 week Phase I randomized, double-blind, placebo-controlled, proof-of-concept trial. Group 1: 0.2mg/kg ixekizumab (N = 19) Group 2: 0.6mg/kg ixekizumab (N = 20) Group 3: 2mg/kg ixekizumab (N = 20) Group 4: Placebo (N = 18)	ACR20 Results at week 10 (primary endpoint): Group 1: 73.7% Group 2: 70% Group 3: 90% (P<0.05) Group 4: 55.6%
Genovese et al. 2014	12 week phase II randomized, double blind, placebo-controlled, dose-ranging trial. BIOLOGIC NAIVE Group 1: 3mg SC ixekizumab (N = 40) Group 2: 10mg SC ixekizumab (N = 35) Group 3: 30mg SC ixekizumab (N= 37) Group 4: 80mg SC ixekizumab (N = 57) Group 5: 180mg SC ixekizumab (N = 37) Group 6: Placebo (N = 54) ANTI-TNF INADEQUATE RESPONDERS Group 1: 80mg SC ixekizumab (N = 65) Group 2: 180mg SC ixekizumab (N = 59) Group 3: Placebo (N = 64)	ACR20 Responses: BIOLOGIC NAIVE Group 1: 45% Group 2: 43% Group 3: 70% (P=0.001) Group 4: 51% Group 5: 54% Group 6: 35% (P=0.001 for 30mg group, P=0.031 for all other groups) ANTI-TNF INADEQUATE RESPONDERS Group 1: 40% Group 2: 39% Group 3: 23% (P<0.05 for all groups)
Martin et al. 2013	85 day phase 1b randomized, double blind, placebo-controlled, multiple-dose trial. Group 1: 50mg SC brodalumab (N = 6) Group 2: 140mg SC brodalumab (N = 6) Group 3: 210mg SC brodalumab (N = 6) Group 4: 420mg IV brodalumab (N = 6) Group 5: 700mg IV brodalumab (N = 6) Group 6: Placebo SC (N = 6) Group 7: Placebo IV (N = 4)	ACR20 Results at Day 85: Group 1: 33% Group 2: 33% Group 3: 17% Group 4: 33% Group 5: 67% Group 6: 33% Group 7: 0% Not statistically significant
Pavelka et al. 2015	12 week randomized, double blind, placebo-controlled, multiple-dose trial of brodalumab (N = 189) vs. placebo (N = 63). Group 1: 70mg SC brodalumab Group 2: 140mg SC brodalumab Group 3: 210mg SC brodalumab Group 4: placebo SC	ACR50 at week 12: Group 1: 16% Group 2: 16% Group 3: 10% Group 4: 13% Not statistically significant

Legend: ACR20 – American College of Rheumatology 20% response criteria; ACR50 – American College of Rheumatology 50% response criteria BD – twice daily; IV – intravenously; N – number of patients; SC – subcutaneously; TNF – tumour necrosis factor.

Secukinumab is a highly selective, fully human immunoglobulin G1k (IgG1k) mAb directed against the IL17A cytokine. Ixekizumab, a humanised IgG4 anti-IL17A mAb, and brodalumab, a fully human IgG2 anti-IL17RA mAb, are also in clinical development and have shown efficacy in autoimmune disease [29-30].

Secukinumab

The first human study of secukinumab was a 16-week RCT where patients received 2 doses of secukinumab at week 0 and 3 versus placebo. The study achieved the primary endpoint, with 54% of patients achieving the ACR20 responses at week 16, compared with 31% in the placebo arm [31].

A phase II RCT did not reach its primary endpoint of achieving a statistically significant ACR20 response at week 16 in the active treatment group compared with placebo [32]. No statistical significance was reached in the HAQ-DI scores comparison between the secukinumab and placebo groups, although there was a greater reduction from baseline in the secukinumab group. The reported rate of AEs was similar between the secukinumab and placebo groups with infection rates not being dose-dependent. The most common infections were nasopharyngitis, upper respiratory tract infection, sinusitis and urinary tract infection. There were no reported cases of immunogenicity.

There are two-phase III secukinumab trials currently in different stages of progress. Both studies are looking at short and long-term efficacy, safety and tolerability of 75 mg and 100 mg secukinumab versus placebo in patients with active RA with an inadequate response to anti-TNF. NURTURE 1, is a RCT with up to one year follow up, which was completed in February 2015 and has pending results [33]. REASSURE 1 study, with up to two years follow up, is estimated to be completed in October 2016 [34].

Ixekizumab

The tolerability and efficacy of ixekizumab, in RA patients taking background oral csDMARDs, has been evaluated in a phase I RCT. Variable SC doses (0.2, 0.6, 2mg/kg) were given every 2 weeks for a total of 5 doses followed by a 16 week evaluation period. ACR20 responses in 90% of patients (statistical significance $p \leq 0.05$) were reached at week 10 with the 2mg/kg dose.

AEs in the ixekizumab groups were not dose related. Leucopenia and vertigo were the most common. AEs in the combined ixekizumab group each occurred in 6.8% of patients. Anti-ixekizumab antibodies were detected in 2 patients with no change in AE or pharmacokinetics. One patient was deemed to have a type III immune mediated reaction [35].

A 12-week phase II RCT investigated the efficacy of ixekizumab in RA patients who were biologic naive or had a prior inadequate response to anti-TNF. ACR20 responses across all varying dose ixekizumab groups were statistically significant in the active treatment arms, with no apparent linear dose response. AEs were of similar frequency with the most common being headache, urinary tract infections (UTIs) and injection site pain/erythema [36].

Brodalumab

A phase 1b [37] and phase II trial [38] have not shown any clinical benefit of brodalumab in RA, and therefore no further clinical trials to assess its efficacy were planned.

INTERLEUKIN 18 (IL18)

IL18 is a cytokine shown to induce chronic inflammation with downstream production of other cytokines such as TNF and GM-CSF [39-40]. Caspase 1 is a protein involved in the cleavage of the IL18 precursor. IL18 has been detected in the synovium of RA patients [40-41]. Arthritis mouse models had more severe disease when primed with IL18 [39], and had reduced disease when IL18 effects were blocked [42]. RA patients have been shown to have high serum levels of IL18, which decreased following treatment with MTX [43]. Phase I trials of a soluble IL18 binding protein, in healthy volunteers and RA patients, displayed dose-dependent pharmacokinetics with a favourable safety profile [44]. A phase II trial investigating an inhibitor of caspase 1, pralnacasan, showed poor results and was terminated due to an animal study showing liver abnormalities [45]. Clinical trials investigating the blockade of IL18 and its receptor are currently in progress in inflammatory disease other than RA.

INTERLEUKIN 20 (IL20)

IL20 and its receptors are upregulated in the synovium of RA patients. Activated monocytes and dendritic cells are the main sources of IL20 via the p38 MAP kinase and nuclear factor – kB (NF-κB) pathway.

NNC0109-0012 is a SC selective anti–IL20 recombinant human mAb that targets and neutralises IL20. A phase IIa proof of concept trial was designed to assess the efficacy, safety, and tolerability of NNC0109-0012 in patients with an inadequate response to MTX [46]. ACR20 responses were found in 59% of patients with efficacy also shown in DAS28-CRP and HAQ-DI parameters. Tolerability profile was acceptable and similar to other biologics.

Subsequent phase IIb trials were terminated/withdrawn as primary and secondary endpoints were not met.

INTERLEUKIN 21 (IL21)

IL21 is produced by activated CD4+ T cells and induces activation of T cells and pro-inflammatory cytokine secretion in RA. IL21 expression correlates with Th17 cell presence in synovial fluid and peripheral blood of RA patients [47-48]. The IL21 receptor has been shown to be produced in RA synovium [49]. Improvement in arthritis has been seen in RA animal models where the IL21/IL21 receptor pathway has been blocked [50].

Phase I and II trials have been conducted in RA patients with results yet to be posted [51-53].

PHOSPHODIESTERASE 4 INHIBITORS

Apremilast (Otezla™, Celgene) [Table 5]

Apremilast is an oral phosphodiesterase 4 inhibitor involved in the inhibition of anti-TNF and other cytokines.

Apremilast has not been shown to be an effective treatment for patients with RA. A phase II study was terminated early due to lack of clinical efficacy [54]. The rate of AEs was similar between the 20mg twice daily (BD) and 30mg BD treatment groups. Diarrhoea and nausea were the most commonly reported AEs.

Weight loss greater than 5% was seen at a higher rate in the apremilast treatment groups compared to placebo.

A second phase II trial was completed in 2014 with results yet to be published [55].

Table 5. Apremilast

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Genovese et al. 2015	24b week phase II, double blind, placebo-controlled, parallel-group trial. Group 1: 20mg BD PO apremilast (N = 82) Group 2: 30mg BD PO apremilast (N = 76) Group 3: Placebo (N = 79)	24 week ACR20, mean change from baseline in HAQ-DI, and total SHS results: Group 1: 19.5%, -0.08, 0.34 Group 2: 27.6%, -0.23, 1.47 Group 3: 24.1%, -0.07, 0.47

Legend: ACR 20 – American College of Rheumatology 20% response criteria; BD – twice daily; HAQ-DI – health assessment questionnaire – damage index; OD – once daily; N – number of patients; PO – oral administration; SHS -Sharp/van der Heijde score.

SMALL MOLECULE INHIBITORS

JANUS KINASE INHIBITORS [TABLE 6]

Baricitinib

Baricitinib is a once-daily, oral, selective Janus kinase (JAK1 and JAK2) inhibitor. The results of 3 phase III trials have been presented at European and American rheumatology conferences in 2015, and are due to be formally published in the near future. These studies have assessed baricitinib to be effective as both monotherapy (RA-BEGIN) [56], and in combination therapy with csDMARDs (RA-BEACON/BUILD) [57-58], in patient groups with an inadequate response to csDMARDs [58] or anti-TNF therapies [57], and limited

or no prior csDMARDs or biologics exposure [56]. HAQ-DI questionnaire and total Sharp score (TSS) were also statistically improved in the active treatment arm. Baricitinib 4mg daily was more effective than 2mg daily dosing. Preliminary reports stated that in a head to head study, baricitinib had shown greater efficacy than adalimumab in patients with an inadequate response to MTX and no prior exposure to biologic therapy (RA-BEAM) [59]. AE rates were similar between baricitinib treatment groups. Recruitment to a long term extension study is still in progress (RA-BEYOND) [60].

Dercenotinib

Dercenotinib is a Janus kinase inhibitor with a five times increased selectivity for JAK3 compared to other JAKs. A phase IIa, 12 week dose-finding RCT of dercenotinib monotherapy [61] in RA patients with an inadequate response to MTX, have shown a statistically significant ACR20 response rates in the active treatment group, in the order of 65% at doses of 50-150mg twice daily. A phase IIb 24 week RCT of dercenotinib therapy in combination with MTX [62] in patients with similar demographics to the phase IIa study, also showed similar statistically significant ACR20 responses in the patient groups treated with 150mg daily and 100mg twice daily.

The mean change from baseline in the DAS28-CRP outcome measure for both studies, and HAQ-DI scores for the IIa study, were also statistically significant in the patient group treated with higher doses. Overall AEs and SAEs were comparable between groups, with a slight preponderance for groups taking higher doses. The most common AEs were headache, nausea, increased infections, liver enzymes and lipids.

Filgotinib

Filgotinib is a selective JAK1 inhibitor. Pharmacokinetic studies have provided evidence of filgotinib efficacy. Two trials using varying doses of filgotinib were conducted in healthy male volunteers [63]. Early clinical data suggested the pharmacokinetics of filgotinib was dose proportional up to 200mg. The maximum pharmacodynamic effect was reached at a daily dose of 200 mg. Dose finding phase IIB studies, of a daily dose range up to 200 mg, are currently under way for monotherapy (DARWIN2) and combination therapy (DARWIN1).

Table 6. Janus Kinase Inhibitors

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Genovese et al. 2015 RA-BEACON	24 week randomised control trial. Group 1: 2mg OD PO baricitinib (N = 174) Group 2: 4mg OD PO baricitinib (N = 177) Group 3: Placebo (N = 176)	12 week ACR20, and HAQ-DI scores Group 1: 49%, 59 Group 2: 55%, 67 (P<0.001) Group 3: 27%, 43
Dougados et al. 2015 RA-BUILD	24 week randomised control trial. Group 1: 2mg od PO baricitinib (N = 229) Group 2: 4mg od PO baricitinib (N = 227) Group 3: Placebo (N = 228)	12 week ACR20, and HAQ-DI scores, 24 week mTSS Group 1: 66% (P<0.001), 64 (P<0.01), 0.33 (P<0.05) Group 2: 62% (P<0.001), 69 (P<0.01), 0.15 (P<0.01) Group 3: 40%, 54, 0.7
Fleischmann et al. 2015 RA-BEGIN	52 week randomised control trial. Group 1: methotrexate (N = 210) Group 2: 4mg od PO baricitinib (N = 159) Group 3: 4mg od PO baricitinib + methotrexate (N = 215)	24 week ACR20 results Group 1: 62% Group 2: 77% Group 3: 78%
Fleischmann et al. 2015	12 week randomized, double blind, placebo-controlled, dose ranging trial. Group 1: 25mg decernotinib BD (N = 41) Group 2: 50mg decernotinib BD (N = 41) Group 3: 100mg decernotinib BD (N = 40) Group 4: 150mg decernotinib BD (N = 41) Group 5: Placebo (N = 41)	Week 12 ACR20, HAQ-DI change from baseline results: Group 1: 39%, -0.24 Group 2: 61.0% (P=0.007), -0.50 (P<0.001) Group 3: 65.0% (P=0.002), -0.52 (P<0.001) Group 4: 65.9% (P=0.002), -0.64 (P<0.001) Group 5: 29.3%, P not available

Legend: ACR 20 – American College of Rheumatology 20% response criteria; BD – twice daily; HAQ-DI – health assessment questionnaire – damage index; OD – once daily; N – number of patients; PO – oral administration.

SPLEEN TYROSINE KINASE (SYK) INHIBITORS

Syk is involved in transmitting signals from classical immunoreceptors such as B- and T cell-receptors on lymphocytes, as well as Fcγ- and Fcε-receptors on myeloid cells and mast cells. Deletion or inhibition of Syk reduces antibody production and inhibits antibody-independent functions of B cells, such as B cell-mediated antigen presentation to T cells [64]. Consequently drugs that inhibit the ATP or the substrate binding P site of Syk have been developed [65], aiming to reduce the inflammatory responses.

Fostamatinib

A 52 week, phase III RCT into varying doses of fostamatinib in combination with MTX showed statistically significant improvements in ACR20 responses (44-49%, compared to 34.2% placebo response), but no clinical significance was demonstrated overall [66]. There were no significant positive radiographic outcomes with fostamatinib. The clinical response was less than expected as earlier phase II trials had shown ACR20 response rates ranging from 57% to 72% [67-68]. Other ongoing trials of fostamatinib were subsequently terminated. A similar side effect profile was shown across the phase II and II trials with the most common side effects being hypertension, diarrhoea and increased hepatic transaminases.

MITOGEN-ACTIVATED PROTEIN (MAP) KINASES

MAP kinase activation induces the expression of multiple genes that together regulate the inflammatory response. The α isoform of p38 MAP kinase is important in the intracellular signaling pathway for the generation of TNF and IL1β [69], therefore p38α inhibitors block the production of TNF and IL1β [70].

Two 12 week RCTs have investigated VX-702, a MAP kinase inhibitor, as a monotherapy, and in combination with MTX in RA patients with an inadequate response to MTX. Though ACR20 response rates were numerically superior with VX-702 compared to placebo, neither study reached statistical significance. Suppression of inflammatory biomarkers was also not sustained past week 4 indicating that p38 MAPK inhibition may not provide sustained

suppression of inflammation in patients with RA. VX-702 has not been developed further as a drug to treat RA [71].

BIO-SIMILARS [TABLE 7]

The European Medicines Agency (EMA) defines biosimilars as "biological medicinal products that contain a version of the active substance of an already authorized, original or 'reference' biological medicinal product.

Evidence on preclinical, pharmacokinetic, pharmacodynamic and clinical data demonstrating comparable efficacy and safety of the biosimilar; its off-patent reference biopharmaceutical is required before a biosimilar is made available on the market [72].

Post-translational modification with changes in cell lines and/or manufacturing processes results in products that are highly similar but not identical to approved 'reference' agents, hence the term 'biosimilar' rather than 'bio-identical'. Minor modification through the manufacturing process may alter function and immunogenicity, therefore raising concerns about switching patients with well controlled disease on reference biologics to biosimilars [73].

A reference drug that is repeatedly interchanged with a similar biological agent might elicit immunogenicity that could compromise the efficacy and safety of both medications. Thus, frequent switching between the original protein product and the biosimilar agent should be avoided, as even subtle differences, such as impurities introduced during manufacturing, can trigger an immune response to biosimilar agents [72].

'Biomimics' or 'biocopies' are versions of mAb or fusion proteins available in countries where regulation is less stringent [74].

It has been estimated that Germany, France and the UK each stand to save between €2.3 billion and €11.7 billion between 2007 and 2020 in response to the introduction of biosimilars [75]. These savings have the potential to be used either to increase the number of patients with access to biologics, or to be diverted into other aspects of care [76].

APPROVED INFLIXIMAB BIOSIMILARS

CT-P13

The efficacy and safety of an infliximab biosimilar (CT-P13) was compared to infliximab in patients with active disease despite MTX therapy. This phase

III randomised controlled non inferiority study demonstrated similar efficacy in DAS28, ACR and EULAR response rates, and low disease or remission rates and all other pharmacokinetic and pharmacodynamic endpoints at week 30. The incidence of drug related AEs were similar (PLANETRA) [77], however the study was not sufficiently powered to detect significant differences in adverse events between the two treatment groups [72].

CT-P13, manufactured by Celltrion Inc., South Korea, is marketed under the trade names Remsima™ (Celltrion Inc.) and Inflectra™ (Hospira Inc., USA). There is also manufacturing via Egis Pharmaceuticals PLC, Hungary who market the drug as Flammegis®. As of May 2015, CT-P13 has been approved for use in approximately 70 countries worldwide [72]. The South Korean MOFDS and the EMA have both approved CT-P13 for the treatment of RA. A phase I study showed similar safety and efficacy in patients with ankylosing spondylitis (PLANETAS) [78], however both these agencies have allowed extrapolation of indications for CT-P13 to six additional diseases for which reference infliximab is approved but in which CT-P13 was not studied, such as psoriatic arthritis and psoriasis.

The first indirect meta-analysis in RA comparing the efficacy and safety of biosimilar-infliximab to other biologicals found no significant difference in efficacy in ACR20 or ACR50 response criteria. In regards to safety and tolerability, the infliximab-biosimilar demonstrated a higher OR than infliximab and other biologics (etanercept, adalimumab, abatacept) suggesting higher chance of occurrence of severe adverse events compared to placebo. However, pairwise comparison did not find any significant difference in safety [79].

Reports from clinical experience [80] and a long term extension RA study [81] have shown comparable clinical effectiveness in patient reported outcomes and disease-activity measures, with no immediate safety signals during one or two years of follow up for patients switched from reference infliximab to CT-P13.

NOR-SWITCH is a randomized double-blind clinical trial currently in progress in Norway. It will compare the safety and efficacy of switching from reference infliximab to CT-P13, with continued treatment with reference infliximab in patients with RA and other autoimmune conditions. NOR-SWITCH is expected to be completed in the first half of 2016 [82-83].

BOW015

BOW015 is an infliximab biosimilar developed by EPIRUS Biopharmaceuticals, Inc. (USA) and manufactured by Reliance Life Sciences

(India) with a trade name of Infimab™. A phase III, double blind, head-to-head comparison of BOW015 and reference infliximab showed similar safety and efficacy in ACR20/50/70 scores. The adverse event rate, mostly infections and infusion reactions, was comparable between treatment groups as was incidence of immunogenicity [84]. To date BOW015 is approved in India alone with plans to file for marketing approval in the UK and US in 2017.

APPROVED ETANERCEPT BIOSIMILAR

HD203

HD203 is an etanercept biosimilar with an amino acid sequence identical to that of reference etanercept product.

A 48 week, phase III randomised controlled, double-blind study of HD203 and reference etanercept, each administered in combination with MTX, has shown similar safety and efficacy profiles with low immunogenicity occurrence [85]. HD203 has been approved by the Korean MOFDS.

APPROVED ADALIMUMAB BIOSIMILAR

ZRC-3197

ZRC-3197 is developed and marketed by Zydus Cadila (India) as Exemptia™. The Cadila Healthcare Laboratory (India) conducted a clinical trial that compared ZRC-3197 and reference adalimumab, in combination with MTX, in 120 RA patients with an inadequate response to MTX. The results of this trial have shown similar ACR20 responses between the 2 groups [86]. ZRC-3197 is currently approved in India alone.

Thus far, phase III clinical trials in the above biosimilars have been promising. The range of biosimilars available on the market will only continue to expand, and the possibility of significant cost savings to various healthcare systems worldwide is an exciting prospect. There are concerns however, regarding the long term safety and efficacy of these drugs, extrapolation to other autoimmune conditions and the right of the physician, over hospital managers, to choose best which patients are suitable or not to switch onto biosimilars.

Table 7. Biosimilars

Author/Date published	Duration, type of study, treatment, number of patients (N)	Main results
Yoo et al. 2013a PLANETRA	30 week phase III randomised, double blind, parallel-group study. Group 1: CT-P13 IV 3mg/kg (N = 302) Group 2: Infliximab IV 3mg/kg (N = 304)	Week 30 ACR20 results: Group 1: 60.9% Group 2: 58.6%
Yoo et al. 2013b	54 week phase III randomised, double blind, parallel group, open label extension trial. Group 1: CT-P13 IV maintenance 3mg/kg (N = 158) Group 2: Infliximab to CT-P13 IV switch 3mg/kg (N = 144)	Week 54 ACR20 results: Group 1: 76.8% Group 2 prior to switch: 77.5% Week 102 ACR20 results: Group 1: 72.2% Group 2 post switch: 71.8% No statistical differences
Kay et al. 2014	54 week phase III randomised, double blind, parallel-group trial of 189 patients. Group 1: BOW015 IV maintenance 3mg/kg Group 2: Infliximab to BOW015 IV switch 3mg/kg	Week 16 ACR20 results: Group 1 BOW015: 89.8%% Group 2 Infliximab prior to switch: 86.4% Week 54 ACR20 results: Group 2: 72.03% No statistical differences
Bae et al. 2014	48 week phase III randomised, double blind, and equivalence trial. Group 1: HD203 SC 25mg twice weekly (N = 147) Group 2: etanercept SC 25mg twice weekly (N = 147)	Week 24 ACR20 results: Group 1: 83.48% Group 2: 81.36% Week 48 ACR20 results: Group 1: 86.27% Group 2: 81.90% No statistical differences
Jani et al. 2015	12 week phase III randomised, double blind, parallel-group trial. Group 1: ZRC-3197 SC 40mg every other week (N = 60) Group 2: Adalimumab SC 40mg every other week (N = 60)	Week 12 ACR20 Results: Group 1: 82.0% Group 2: 79.2%

Legend: ACR 20 – American College of Rheumatology 20% response criteria; BD – twice daily; IV – intravenously; N – number of patients; SC – subcutaneously.

RITUXIMAB BIOSIMILAR

PF-05280586

PF-05280586 is a proposed biosimilar to rituximab and marketed by Pfizer. A double-blind phase I/II pharmacokinetic (PK) similarity trial compared PF-05280586 to rituximab sourced from the European Union (rituximab-EU) and United States (rituximab-US).

Although not designed to demonstrate similarity for efficacy, mean DAS28-CRP, mean number of tender and swollen joint counts, and mean high-sensitivity CRP values decreased over time, and improvement in ACR20/50/70 scores were seen in all groups.

All 3 treatments had similar effect on CD19+ B cells. All treatments were generally well-tolerated, with similar AE profiles. These results support continued clinical development of PF-05280586 as a potential biosimilar to rituximab [87].

CONCLUSION

Impressive advances in the research associated with the aetiopathogenesis of RA led to the discovery of new molecules and inflammatory pathways, which play an important role in the disease inflammatory processes and irreversible joint damage. An ever-increasing pool of potential new cytokine targeted therapies is in development, with some showing promising data. However, it is too early to determine if all these new biologic agents will be translated into licensed therapies for RA.

As ever, the cost implications of such treatments can limit which patients have access to these drugs, especially in countries without free access to healthcare. Biosimilars offer an exciting chance to reduce the cost of treating RA, but it is important to remember that these drugs are only similar and not the same as current biologic treatments. Therefore, they should be used with caution. The patents for many biologic agents currently used in the treatment of RA will expire by the end of 2018. It is expected that many more biosimilars will be made available by then. There should still be opportunities for new biologic drugs, as long as they can demonstrate superior efficacy to current available biologics with acceptable safety profiles [88]. As highlighted in this chapter, many new therapeutic targets seem promising as potential new agents

for RA treatment, according to data derived from early phase trials, but they still have to prove their therapeutic potential in larger clinical trials. The landscape of RA treatment is ever changing and this is definitely an exciting time for research within the field of RA.

ACKNOWLEDGMENTS

The authors will like to thank to Dr. Maria Leandro, Senior Lecturer and Consultant Rheumatologist, University College London, Department of Inflammation, Infection and Immunity (email:maria.leandro@ucl.ac.uk), for reviewing this chapter.

.

REFERENCES

[1] Østergaard, M; Baslund, B; Rigby, W; Rojkovich, B; Jorgensen, C; Dawes, PT; Wiell, C; Wallace, DJ; Tamer, SC; Kastberg, H; Petersen, J; Sierakowski, S. "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.*, vol. 62, no. 8, pp. 2227–38, Aug. 2010.

[2] Taylor, PC; Quattrocchi, E; Mallett, S; Kurrasch, R; Petersen, J; Chang, DJ. "Ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naive, rheumatoid arthritis patients with an inadequate response to methotrexate: a randomised, double-blind, placebo-controlled clinical trial.," *Ann. Rheum. Dis.*, vol. 70, no. 12, pp. 2119–25, Dec. 2011.

[3] Beum, PV; Lindorfer, MA; Beurskens, F; Stukenberg, PT; Lokhorst, HM; Pawluczkowycz, AW; Parren, PWHI; van de Winkel, JGJ; Taylor, RP. "Complement activation on B lymphocytes opsonized with rituximab or ofatumumab produces substantial changes in membrane structure preceding cell lysis.," *J. Immunol.*, vol. 181, no. 1, pp. 822–32, Jul. 2008.

[4] GlaxoSmithKline, "Investigating Clinical Efficacy of Ofatumumab in Adult Rheumatoid Arthritis (RA) Patients Who Had an Inadequate Response to MTX Therapy."

[5] GlaxoSmithKline, "Investigating Clinical Efficacy of Ofatumumab in Adult Rheumatoid Arthritis (RA) Patients Who Had an Inadequate Response to TNF-α Antagonist Therapy."

[6] Kurrasch, R; Brown, JC; Chu, M; Craigen, J; Overend, P; Patel, B; Wolfe, S; Chang, DJ. "Subcutaneously administered ofatumumab in rheumatoid arthritis: a phase I/II study of safety, tolerability, pharmacokinetics, and pharmacodynamics.," *J. Rheumatol.*, vol. 40, no. 7, pp. 1089–96, Jul. 2013.

[7] Rigby, W; Tony, HP; Oelke, K; Combe, B; Laster, A; von Muhlen, CA; Fisheleva, E; Martin, C; Travers, H; Dummer, W. "Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial.," *Arthritis Rheum.*, vol. 64, no. 2, pp. 350–9, Feb. 2012.

[8] Tak, PP; Mease, PJ; Genovese, MC; Kremer, J; Haraoui, B; Tanaka, Y; Bingham, CO; Ashrafzadeh, A; Travers, H; Safa-Leathers, S; Kumar, S; Dummer, W. "Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to at least one tumor necrosis factor inhibitor: results of a forty-eight–week randomized, double-blind, placebo-controlled, parallel-group phase III trial," *Arthritis Rheum.*, vol. 64, no. 2, pp. 360–70, Feb. 2012.

[9] Harigai, M; Tanaka, Y; Maisawa, S. "Safety and efficacy of various dosages of ocrelizumab in Japanese patients with rheumatoid arthritis with an inadequate response to methotrexate therapy: a placebo-controlled double-blind parallel-group study.," *J. Rheumatol.*, vol. 39, no. 3, pp. 486–95, Mar. 2012.

[10] C. go. I. NCT01390545, "VELVET, a Dose Range Finding Trial of Veltuzumab in Subjects With Moderate to Severe Rheumatoid Arthritis - Full Text View - ClinicalTrials.gov."

[11] Helling, B; König, M; Dälken, B; Engling, A; Krömer, W; Heim, K; Wallmeier, H; Haas, J; Wildemann, B; Fritz, B; Jonuleit, H; Kubach, J; Dingermann, T; Radeke, HH; Osterroth, F; Uherek, C; Czeloth, N; Schüttrumpf, J. "A specific CD4 epitope bound by tregalizumab mediates activation of regulatory T cells by a unique signaling pathway.," *Immunol. Cell Biol.*, vol. 93, no. 4, pp. 396–405, Apr. 2015.

[12] et al. Rudnev, Anatoliy; Ragavan, Sukanya; Trollmo, Christina; Malmstroem, Vivianne; Becker, Christian; Jonuleit, Helmut. "Selective Activation of Naturally Occurring Regulatory T Cells (Tregs) by the Monoclonal Antibody (mAb) BT-061. Markers of Clinical Activity and

Early Phase II Results in Patients with Rheumatoid Arthritis (RA)," *Arthritis Rheum*, vol. 62, no. Suppl 10, p. 1125, 2010.

[13] "Study to Investigate the Safety and Efficacy of Tregalizumab in Subjects (MTX-IR) With Active Rheumatoid Arthritis."

[14] Isaacs, JD; Manna, VK; Rapson, N; Bulpitt, KJ; Hazleman, BL; Matteson, EL; St Clair, EW; Schnitzer, TJ; Johnston, JM. "CAMPATH-1H in rheumatoid arthritis--an intravenous dose-ranging study.," *Br. J. Rheumatol.*, vol. 35, no. 3, pp. 231–40, Mar. 1996.

[15] Weinblatt, ME; Maddison, PJ; Bulpitt, KJ; Hazleman, BL; Urowitz, MB; Sturrock, RD; Coblyn, JS; Maier, AL; Spreen, WR; Manna, VK; Johnston, JM. "Campath-1h, a humanized monoclonal antibody, in refractory rheumatoid arthritis," *Arthritis Rheum.*, vol. 38, no. 11, pp. 1589–1594, Nov. 1995.

[16] Anderson, AE; Lorenzi, AR; Pratt, A; Wooldridge, T; Diboll, J; Hilkens, CMU; Isaacs, JD. "Immunity 12 years after alemtuzumab in RA: $CD5^+$ B cell depletion, thymus-dependent T cell reconstitution and normal vaccine responses.," *Rheumatology (Oxford).*, vol. 51, no. 8, pp. 1397–406, Aug. 2012.

[17] Coclet-Ninin, J; Dayer, JM; Burger, D. "Interferon-beta not only inhibits interleukin-1beta and tumor necrosis factor-alpha but stimulates interleukin-1 receptor antagonist production in human peripheral blood mononuclear cells.," *Eur. Cytokine Netw.*, vol. 8, no. 4, pp. 345–9, Dec. 1997.

[18] Palmer, G; Mezin, F; Juge-Aubry, CE; Plater-Zyberk, C; Gabay, C; Guerne, PA. "Interferon beta stimulates interleukin 1 receptor antagonist production in human articular chondrocytes and synovial fibroblasts.," *Ann. Rheum. Dis.*, vol. 63, no. 1, pp. 43–9, Jan. 2004.

[19] van Holten, J; Pavelka, K; Vencovsky, J; Stahl, H; Rozman, B; Genovese, M; Kivitz, AJ; Alvaro, J; Nuki, G; Furst, DE; Herrero-Beaumont, G; McInnes, IB; Musikic, P; Tak, PP. "A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis.," *Ann. Rheum. Dis.*, vol. 64, no. 1, pp. 64–9, Jan. 2005.

[20] Burmester, GR; Weinblatt, ME; McInnes, IB; Porter, D; Barbarash, O; Vatutin, M; Szombati, I; Esfandiari, E; Sleeman, MA; Kane, CD; Cavet, G; Wang, B; Godwood, A; Magrini, F. "Efficacy and safety of mavrilimumab in subjects with rheumatoid arthritis.," *Ann. Rheum. Dis.*, vol. 72, no. 9, pp. 1445–52, Sep. 2013.

[21] Takeuchi, T; Tanaka, Y; Close, D; Godwood, A; Wu, CY; Saurigny, D. "Efficacy and safety of mavrilimumab in Japanese subjects with rheumatoid arthritis: findings from a Phase IIa study.," *Mod. Rheumatol.*, vol. 25, no. 1, pp. 21–30, Jan. 2015.

[22] MedImmuneLtd, "A Study of Mavrilimumab Versus Anti Tumor Necrosis Factor in Subjects With Rheumatoid Arthritis. ClinicalTrials.gov Identifier: NCT01715896."

[23] Gaffen, SL; Jain, R; Garg, AV; Cua, DJ. "The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing.," *Nat. Rev. Immunol.*, vol. 14, no. 9, pp. 585–600, Sep. 2014.

[24] Smolen, J; Agarwal, SK; Ilivanova, E; Xu, XL; Miao, Y; Mudivarthy, S; Xu, W; Radziszewski, W; Greenspan, A; Beutler, A; Baker, D. "OP0031 A Phase 2 Study Evaluating the Efficacy and Safety of Subcutaneously Administered Ustekinumab and Guselkumab in Patients with Active Rheumatoid Arthritis Despite Treatment with Methotrexate:," *Ann. Rheum. Dis.*, vol. 74, no. Suppl 2, pp. 76.2–77, Jun. 2015.

[25] Baslund, B; Tvede, N; Danneskiold-Samsoe, B; Larsson, P; Panayi, G; Petersen, J; Petersen, LJ; Beurskens, FJM; Schuurman, J; van de Winkel, JGJ; Parren, PWHI; Gracie, JA; Jongbloed, S; Liew, FY; McInnes, IB. "Targeting interleukin-15 in patients with rheumatoid arthritis: a proof-of-concept study.," *Arthritis Rheum.*, vol. 52, no. 9, pp. 2686–92, Oct. 2005.

[26] Nakae, S; Nambu, A; Sudo, K; Iwakura, Y. "Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice.," *J. Immunol.*, vol. 171, no. 11, pp. 6173–7, Dec. 2003.

[27] Lubberts, E; Koenders, MI; Oppers-Walgreen, B; van den Bersselaar, L; Coenen-de Roo, CJJ; Joosten, LAB; van den Berg, WB. "Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion," *Arthritis Rheum.*, vol. 50, no. 2, pp. 650–659, Feb. 2004.

[28] Plater-Zyberk, C; Joosten, LAB; Helsen, MMA; Koenders, MI; Baeuerle, PA; van den Berg, WB. "Combined blockade of granulocyte-macrophage colony stimulating factor and interleukin 17 pathways potently suppresses chronic destructive arthritis in a tumour necrosis factor alpha-independent mouse model.," *Ann. Rheum. Dis.*, vol. 68, no. 5, pp. 721–8, May 2009.

[29] Patel, DD; Lee, DM; Kolbinger, F; Antoni, C. "Effect of IL-17A blockade with secukinumab in autoimmune diseases.," *Ann. Rheum. Dis.*, vol. 72 Suppl 2, pp. ii116–23, Apr. 2013.

[30] Kellner, H. "Targeting interleukin-17 in patients with active rheumatoid arthritis: rationale and clinical potential.," *Ther. Adv. Musculoskelet. Dis.*, vol. 5, no. 3, pp. 141–52, Jun. 2013.

[31] Hueber, W; Patel, DD; Dryja, T; Wright, AM; Koroleva, I; Bruin, G; Antoni, C; Draelos, Z; Gold, MH; Durez, P; Tak, PP; Gomez-Reino, JJ; Foster, CS; Kim, RY; Samson, CM; Falk, NS; Chu, DS; Callanan, D; Nguyen, QD; Rose, K; Haider, A; Di Padova, F. "Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis.," *Sci. Transl. Med.*, vol. 2, no. 52, p. 52ra72, Oct. 2010.

[32] Genovese, MC; Durez, P; Richards, HB; Supronik, J; Dokoupilova, E; Mazurov, V; Aelion, JA; Lee, SH; Codding, CE; Kellner, H; Ikawa, T; Hugot, S; Mpofu, S. "Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study," *Ann. Rheum. Dis.*, vol. 72, no. 6, pp. 863–869, Jun. 2012.

[33] Novartis, "Efficacy at 24 Weeks and Safety, Tolerability and Long Term Efficacy up to 1 Year of Secukinumab (AIN457) in Patients With Active Rheumatoid Arthritis (RA) and an Inadequate Response to Anti-Tumor Necrosis Factor α (Anti-TNFα) Agents. (NURTURE 1)."

[34] Novartis, "Efficacy at 24 Weeks and Safety, Tolerability and Long Term Efficacy up to 2 Years of Secukinumab (AIN457) in Patients With Active Rheumatoid Arthritis and an Inadequate Response to Anti-TNFα Agents (REASSURE)."

[35] Genovese, MC; Van den Bosch, F; Roberson, SA; Bojin, S; Biagini, IM; Ryan, P; Sloan-Lancaster, J. "LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study.," *Arthritis Rheum.*, vol. 62, no. 4, pp. 929–39, Apr. 2010.

[36] Genovese, M; Greenwald, M; Cho, CS; Berman, A; Jin, L; Cameron, G; Wang, L; Xie, L; Braun, D; Berclaz, PY; Banerjee, S. "OP0021 A phase 2 study of multiple subcutaneous doses of LY2439821, an anti-IL-17 monoclonal antibody, in patients with rheumatoid arthritis in two populations: Naive to biologic therapy or inadequate responders to tumor necrosis factor alpha inhibitors," *Ann. Rheum. Dis.*, vol. 71, no. Suppl 3, pp. 59–59, Jan. 2014.

[37] Martin, DA; Churchill, M; Flores-Suarez, L; Cardiel, MH; Wallace, D; Martin, R; Phillips, K; Kaine, JL; Dong, H; Salinger, D; Stevens, E;

Russell, CB; Chung, JB. "A phase Ib multiple ascending dose study evaluating safety, pharmacokinetics, and early clinical response of brodalumab, a human anti-IL-17R antibody, in methotrexate-resistant rheumatoid arthritis.," *Arthritis Res. Ther.*, vol. 15, no. 5, p. R164, Jan. 2013.

[38] Pavelka, K; Chon, Y; Newmark, R; Lin, SL; Baumgartner, S; Erondu, N. "A study to evaluate the safety, tolerability, and efficacy of brodalumab in subjects with rheumatoid arthritis and an inadequate response to methotrexate.," *J. Rheumatol.*, vol. 42, no. 6, pp. 912–9, Jun. 2015.

[39] Leung, BP; McInnes, IB; Esfandiari, E; Wei, XQ; Liew, FY. "Combined effects of IL-12 and IL-18 on the induction of collagen-induced arthritis.," *J. Immunol.*, vol. 164, no. 12, pp. 6495–502, Jun. 2000.

[40] McInnes, IB; Gracie, JA; Leung, BP; Wei, XQ; Liew, FY. "Interleukin 18: a pleiotropic participant in chronic inflammation.," *Immunol. Today*, vol. 21, no. 7, pp. 312–5, Jul. 2000.

[41] Gracie, JA; Forsey, RJ; Chan, WL; Gilmour, A; Leung, BP; Greer, MR; Kennedy, K; Carter, R; Wei, XQ; Xu, D; Field, M; Foulis, A; Liew, FY; McInnes, IB. "A proinflammatory role for IL-18 in rheumatoid arthritis.," *J. Clin. Invest.*, vol. 104, no. 10, pp. 1393–401, Dec. 1999.

[42] Wei, XQ; Leung, BP; Arthur, HM; McInnes, IB; Liew, FY. "Reduced incidence and severity of collagen-induced arthritis in mice lacking IL-18.," *J. Immunol.*, vol. 166, no. 1, pp. 517–21, Jan. 2001.

[43] Bresnihan, B; Roux-Lombard, P; Murphy, E; Kane, D; FitzGerald, O; Dayer, JM. "Serum interleukin 18 and interleukin 18 binding protein in rheumatoid arthritis.," *Ann. Rheum. Dis.*, vol. 61, no. 8, pp. 726–9, Aug. 2002.

[44] Tak, PP; Bacchi, M; Bertolino, M. "Pharmacokinetics of IL-18 binding protein in healthy volunteers and subjects with rheumatoid arthritis or plaque psoriasis.," *Eur. J. Drug Metab. Pharmacokinet.*, vol. 31, no. 2, pp. 109–16, Jan.

[45] RJ; et al. Pavelka, K; Kuba, V. "Clinical effects of pralnacasan (PRAL), an orally active interleukin-1 beta converting enzyme (ICE) inhibitor in 285 patients PhII trial in rheumatoid arthritis 9abstract]," *Am. Coll. Rheumatol. 66th Annu. Sci. Meet. New Orleans*.

[46] Šenolt, L; Leszczynski, P; Dokoupilová, E; Göthberg, M; Valencia, X; Hansen, BB; Cañete, JD. "Efficacy and Safety of Anti-Interleukin-20 Monoclonal Antibody in Patients With Rheumatoid Arthritis: A Randomized Phase IIa Trial.," *Arthritis Rheumatol. (Hoboken, N.J.)*, vol. 67, no. 6, pp. 1438–48, Jul. 2015.

[47] Niu, X; He, D; Zhang, X; Yue, T; Li, N; Zhang, JZ; Dong, C; Chen, G. "IL-21 regulates Th17 cells in rheumatoid arthritis.," *Hum. Immunol.*, vol. 71, no. 4, pp. 334–41, May 2010.

[48] Yuan, FL; Hu, W; Lu, WG; Li, X; Li, JP; Xu, RS; Li, CW; Chen, FH; Jin, C. "Targeting interleukin-21 in rheumatoid arthritis.," *Mol. Biol. Rep.*, vol. 38, no. 3, pp. 1717–21, Mar. 2011.

[49] Jüngel, A; Distler, JHW; Kurowska-Stolarska, M; Seemayer, CA; Seibl, R; Forster, A; Michel, BA; Gay, RE; Emmrich, F; Gay, S; Distler, O. "Expression of interleukin-21 receptor, but not interleukin-21, in synovial fibroblasts and synovial macrophages of patients with rheumatoid arthritis.," *Arthritis Rheum.*, vol. 50, no. 5, pp. 1468–76, May 2004.

[50] Young, DA; Hegen, M; Ma, HLM; Whitters, MJ; Albert, LM; Lowe, L; Senices, M; Wu, PW; Sibley, B; Leathurby, Y; Brown, TP; Nickerson-Nutter, C; Keith, JC; Collins, M. "Blockade of the interleukin-21/interleukin-21 receptor pathway ameliorates disease in animal models of rheumatoid arthritis.," *Arthritis Rheum.*, vol. 56, no. 4, pp. 1152–63, May 2007.

[51] Novo Nordisk, "First-in-Man Trial of NNC114-0005 in Healthy Subjects and Subjects With Rheumatoid Arthritis."

[52] Novo Nordisk, "A Randomised, Double-blind, Placebo-controlled, Parallel-group Trial to Assess Clinical Efficacy of NNC0114-0006 in Subjects With Active Rheumatoid Arthritis."

[53] Novo Nordisk, "Safety and Tolerability of NNC0114-0006 at Increasing Dose Levels in Subjects With Rheumatoid Arthritis."

[54] Genovese, MC; Jarosova, K; Cieślak, D; Alper, J; Kivitz, A; Hough, DR; Maes, P; Pineda, L; Chen, M; Zaidi, F. "Apremilast in Patients With Active Rheumatoid Arthritis: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study.," *Arthritis Rheumatol. (Hoboken, N.J.)*, vol. 67, no. 7, pp. 1703–10, Jul. 2015.

[55] Baylor Research Institute, "The Controlled Trial of Apremilast for Rheumatoid Arthritis Treatment (CARAT)."

[56] Keystone, EC; Taylor, PC; Drescher, E; Schlichting, DE; Beattie, SD; Berclaz, PY; Lee, CH; Fidelus-Gort, RK; Luchi, ME; Rooney, TP; Macias, WL; Genovese, MC. "Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate.," *Ann. Rheum. Dis.*, vol. 74, no. 2, pp. 333–40, Feb. 2015.

[57] Genovese, MC; Kremer, J; Zamani, O; Ludivico, C; Krogulec, M; Xie, L; Beattie, S; Koch, AE; Cardillo, T; Rooney, T; Macias, W; Schlichting, D;

Smolen, JS. "OP0029 Baricitinib, An Oral Janus Kinase (JAK)1/JAK2 Inhibitor, in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to TNF Inhibitors: Results of the Phase 3 RA-Beacon Study:," *Ann. Rheum. Dis.*, vol. 74, no. Suppl 2, pp. 75.3–76, Jun. 2015.

[58] Dougados, M; van der Heijde, D; Chen, YC; Greenwald, M; Drescher, E; Liu, J; Beattie, S; de la Torre, I; Rooney, T; Schlichting, D; de Bono, S; Emery, P. "LB0001 Baricitinib, an Oral Janus Kinase (JAK)1/JAK2 Inhibitor, in Patients with Active Rheumatoid Arthritis (RA) and An Inadequate Response to CDMARD Therapy: Results of the Phase 3 RA-Build Study:," *Ann. Rheum. Dis.*, vol. 74, no. Suppl 2, pp. 79.2–79, Jun. 2015.

[59] Lilly, "https://investor.lilly.com/releasedetail.cfm?ReleaseID=936515."

[60] EL. Company, "An Extension Study in Participants With Moderate to Severe Rheumatoid Arthritis (RA-BEYOND). ClinicalTrials.gov Identifier: NCT01885078."

[61] Fleischmann, RM; Damjanov, NS; Kivitz, AJ; Legedza, A; Hoock, T; Kinnman, N. "A randomized, double-blind, placebo-controlled, twelve-week, dose-ranging study of decernotinib, an oral selective JAK-3 inhibitor, as monotherapy in patients with active rheumatoid arthritis.," *Arthritis Rheumatol. (Hoboken, N.J.)*, vol. 67, no. 2, pp. 334–43, Feb. 2015.

[62] Genovese, MC; van Vollenhoven, RF; Pacheco-Tena, C; Zhang, Y; Kinnman, N. "VX-509 (Decernotinib), an Oral Selective JAK-3 Inhibitor, in Combination With Methotrexate in Patients With Rheumatoid Arthritis," *Arthritis Rheumatol.*, vol. 68, no. 1, pp. 46–55, Jan. 2016.

[63] Namour, F; Diderichsen, PM; Cox, E; Vayssière, B; Van der Aa, A; Tasset, C; Van't Klooster, G. "Pharmacokinetics and Pharmacokinetic/ Pharmacodynamic Modeling of Filgotinib (GLPG0634), a Selective JAK1 Inhibitor, in Support of Phase IIB Dose Selection.," *Clin. Pharmacokinet.*, vol. 54, no. 8, pp. 859–74, Aug. 2015.

[64] Gomez-Puerta, JA; Mócsai, A. "Tyrosine kinase inhibitors for the treatment of rheumatoid arthritis.," *Curr. Top. Med. Chem.*, vol. 13, no. 6, pp. 760–73, Jan. 2013.

[65] OJD; Uckun, FM. "Targeting Spleen Tyrosine Kinase (Syk) for Treatment of Human Disease," *Pharm. Drug Deliv. Res.*

[66] Weinblatt, ME; Genovese, MC; Ho, M; Hollis, S; Rosiak-Jedrychowicz, K; Kavanaugh, A; Millson, DS; Leon, G; Wang, M; van der Heijde, D. "Effects of fostamatinib, an oral spleen tyrosine kinase inhibitor, in

rheumatoid arthritis patients with an inadequate response to methotrexate: results from a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.," *Arthritis Rheumatol. (Hoboken, N.J.)*, vol. 66, no. 12, pp. 3255–64, Dec. 2014.

[67] Weinblatt, ME; Kavanaugh, A; Burgos-Vargas, R; Dikranian, AH; Medrano-Ramirez, G; Morales-Torres, JL; Murphy, FT; Musser, TK; Straniero, N; Vicente-Gonzales, AV; Grossbard, E. "Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial.," *Arthritis Rheum.*, vol. 58, no. 11, pp. 3309–18, Dec. 2008.

[68] 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.*, vol. 363, no. 14, pp. 1303–12, Oct. 2010.

[69] Herlaar, E; Brown, Z. "p38 MAPK signalling cascades in inflammatory disease.," *Mol. Med. Today*, vol. 5, no. 10, pp. 439–47, Oct. 1999.

[70] Arthur, JSC; Ley, SC. "Mitogen-activated protein kinases in innate immunity.," *Nat. Rev. Immunol.*, vol. 13, no. 9, pp. 679–92, Sep. 2013.

[71] Damjanov, N; Kauffman, RS; Spencer-Green, GT. "Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies.," *Arthritis Rheum.*, vol. 60, no. 5, pp. 1232–41, May 2009.

[72] Dörner, T; Kay, J. "Biosimilars in rheumatology: current perspectives and lessons learnt.," *Nat. Rev. Rheumatol.*, vol. 11, no. 12, pp. 713–24, Dec. 2015.

[73] "British Society for Rheumatology Position statement on biosimilar medicines (February 2015)."

[74] Dörner, T; Strand, V; Castañeda-Hernández, G; Ferraccioli, G; Isaacs, JD; Kvien, TK; Martin-Mola, E; Mittendorf, T; Smolen, JS; Burmester, GR. "The role of biosimilars in the treatment of rheumatic diseases.," *Ann. Rheum. Dis.*, vol. 72, no. 3, pp. 322–8, Mar. 2013.

[75] Haustein, R; de Millas, C; Ariane Höer, M; Professor Bertram Häussler, M. "Saving money in the European healthcare systems with biosimilars," *Generics Biosimilars Initiat. J.*, vol. 1, no. 3–4, pp. 120–126, Nov. 2012.

[76] Gulácsi, L; Brodszky, V; Baji, P; Kim, H; Kim, SY; Cho, YY; Péntek, M. "Biosimilars for the management of rheumatoid arthritis: economic considerations.," *Expert Rev. Clin. Immunol.*, vol. 11 Suppl 1, pp. S43–52, Jan. 2015.

[77] Yoo, DH; Hrycaj, P; Miranda, P; Ramiterre, E; Piotrowski, M; Shevchuk, S; Kovalenko, V; Prodanovic, N; Abello-Banfi, M; Gutierrez-Urena, S; Morales-Olazabal, L; Tee, M; Jimenez, R; Zamani, O; Lee, SJ; Kim, H; Park, W; Muller-Ladner, U. "A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study," *Ann. Rheum. Dis.*, vol. 72, no. 10, pp. 1613–1620, May 2013.

[78] Park, W; Hrycaj, P; Jeka, S; Kovalenko, V; Lysenko, G; Miranda, P; Mikazane, H; Gutierrez-Ureña, S; Lim, M; Lee, YA; Lee, SJ; Kim, H; Yoo, DH; Braun, J. "A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study.," *Ann. Rheum. Dis.*, vol. 72, no. 10, pp. 1605–12, Oct. 2013.

[79] Baji, P; Péntek, M; Czirják, L; Szekanecz, Z; Nagy, G; Gulácsi, L; Brodszky, V. "Efficacy and safety of infliximab-biosimilar compared to other biological drugs in rheumatoid arthritis: a mixed treatment comparison.," *Eur. J. Health Econ.*, vol. 15 Suppl 1, pp. S53–64, May 2014.

[80] Nikiphorou, E; Kautiainen, H; Hannonen, P; Asikainen, J; Kokko, A; Rannio, T; Sokka, T. "Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data.," *Expert Opin. Biol. Ther.*, vol. 15, no. 12, pp. 1677–83, Dec. 2015.

[81] PW; MLU; Yoo, D; Prodanovic, N; Jaworski, J; Miranda, P; Ramiterre, EB; Lanzon, A; Baranauskaite, A; Wiland, P; Abud-Mendoza, C; Oparanov, B; Smiyan, S; Son, YK. "Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13," *Arthritis Rheum.*, vol. 65, no. 12, p. 3319, 2013.

[82] Diakonhjemmet Hospital, "The NOR-SWITCH Study," p. ClinicalTrials.gov Identifier: NCT02148640.

[83] Isaacs, JD; Cutolo, M; Keystone, EC; Park, W; Braun, J. "Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody.," *J. Intern. Med.*, vol. 279, no. 1, pp. 41–59, Sep. 2015.

[84] WM; Kay, J; Chopra, A; Lassen, C; Shneyer, L. "BOW015, A BIOSIMILAR INFLIXIMAB: DISEASE ACTIVITY AND DISABILITY OUTCOMES FROM A PHASE 3 ACTIVE COMPARATOR STUDY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS ON STABLE METHOTREXATE DOSES," *Ann Rheum Dis*, vol. 74, no. Suppl 2, p. 462, 2015.

[85] Bae, SC; Kim, JS; Choe, JY; Park, W; Lee, SR; Ahn, Y; Seo, Y. "OP0011 A Randomized, Double-Blind, Phase 3 Equivalence TRIAL Comparing the Etanercept Biosimilar, Hd203, with Enbrel(R), in Combination with Methotrexate (MTX) in Patients with Rheumatoid Arthritis (RA)," *Ann. Rheum. Dis.*, vol. 73, no. Suppl 2, pp. 63–64, Jun. 2014.

[86] Jani, RH; Gupta, R; Bhatia, G; Rathi, G; Ashok Kumar, P; Sharma, R; Kumar, U; Gauri, LA; Jadhav, P; Bartakke, G; Haridas, V; Jain, D; Mendiratta, SK. "A prospective, randomized, double-blind, multicentre, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (Exemptia; ZRC-3197) and adalimumab (Humira) in patients with rheumatoid arthritis.," *Int. J. Rheum. Dis.*, Jul. 2015.

[87] Jacobs, I; Yin, D; Melia, LA; Gumbiner, B; Suster, M; Thomas, D; Meng, X. "SAT0190 A Phase I Trial Comparing PF-05280586 (A Potential Biosimilar) and Rituximab in Patients with Active Rheumatoid Arthritis," *Ann. Rheum. Dis.*, vol. 74, no. Suppl 2, pp. 724.1–724, Jun. 2015.

[88] Polmar, SH. "New drugs for rheumatoid arthritis: The industry point of view.," *Reumatol. Clin.*, vol. 6, no. 1, pp. 3–4, Jan. 2010.