Review Article

Impact of Biological DMARDS on Quality of Life of Rheumatoid Arthritis Patients– A Narrative Review

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ABSTARCT

The purpose of this review was to evaluate the efficacy of each biological Disease Modifying Anti Rheumatic Drugs (DMARDs) (adalimumab, anakinra, infliximab, rituximab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, tofacitinib) in improving the quality of life of Rheumatoid Arthritis (RA) patients. Biological DMARDs are genetically-engineered proteins derived from human genes, designed to inhibit certain components of the immune system, which is effective in the treatment of patients with RA. Randomized control trials on each of the biological DMARDs were searched on PubMed. Only articles which have the health-related quality of life measures and complete data were included. In this review, the health quality assessment evaluated was based on HAQ, SF-36, Pain VAS and MOS-Sleep. In conclusion, all biological DMARDs showed significant improvement based on the health assessment tools in both monotherapy and combination therapy with conventional DMARDs in the treatment of RA.

Keywords: biologic DMARDs, patient-reported outcomes, quality of life, rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) represents a chronic systemic inflammatory disease of an unknown cause. The annual incidence of RA is approximately 0.03%, and the rate of prevalence is approximately 1%, which is occurring between the ages of 35 to 50 years. [1] Goals of RA treatment are mainly to control disease activity and slow down the rate of joint damage, along with minimizing pain, stiffness, inflammation, and complications leading to improvement in quality of life.

Disease-modifying antirheumatic drugs (DMARDs) are commonly used in the treatment of RA through the suppression of body's overactive immune and inflammatory systems. DMARDs normally require up to weeks or months for the effects to take place, which is unsuitable for immediate symptomatic relief. DMARDs can be classified into non-biologic and biologic agents. Non-biologic DMARDs include hydroxychloroquine, azathioprine, sulfasalazine, leflunomide, cyclosporine, and finally methotrexate (MTX) which represents the gold standard in the treatment of RA. Biologic DMARDs can be further divided into tumor necrosis factor inhibitors (TNF-inhibitors), interleukin-6 (IL-6) inhibitors, T-cell costimulatory blocking agents, B cell depleting agents, interleukin-1 (IL-1) receptor blockers, and Janus kinase enzyme inhibitors. TNF-inhibitors include etanercept, certolizumab, golimumab, infliximab, and adalimumab. Tocilizumab is an IL-6 inhibitor, while anakinra is an IL-1 receptor blocker. Abatacept targets T cells (T-cell costimulatory blocking agent), while rituximab targets B cells (B cell depleting agent). Lastly, tofacitinib inhibits the Janus kinase enzyme.

TNF-inhibitors can be either monoclonal anti-TNF antibodies or soluble TNF receptors (etanercept). Either strategy would bind to TNF thus preventing it from engaging with cell membrane-TNF receptors and activate inflammatory pathways. Tocilizumab is a competitive antagonist of IL-6 for its receptor thus inhibiting the proinflammatory effects of this cytokine. Similarly for anakinra which is also a receptor antagonist for IL-1. Abatacept is a soluble recombinant protein which binds to antigen presenting cells thus inhibiting the CD28 and CD80/CD86 costimulatory signal necessary for T-cell activation, while rituximab

binds to the CD20 receptor on B cells thus inducing cell death. Tofacitinib works by binding to adenosine triphosphate (ATP) binding site of Janus kinase enzyme which is responsible for activation of gene transcription. This leads to decreased cytokine production and modulation of immune response.

The improvement in the quality of life represents one of the main treatment goals in RA patients. In order to assess the quality of life, different questionnaires or tools of different parameters were used to determine the effects of drugs on patient's overall well-being. The commonly used tools for quality of life assessment in RA include HAQ-DI, SF-36, fatigue/ pain VAS, and sleep-MOS measure.

HAQ-DI

The most commonly used Health Assessment Questionnaire is the HAQ Disability Index (HAQ-DI), a component of HAQ which assesses a patient's level of functional ability. [2] The 20 questions are designed to evaluate performance in daily functions like dressing, walking, eating etc., which are scored on 4 level difficulty score leading to understand the patient's disability. Overall score will be calculated by averaging all 8 category scores. Score of 0-1 indicates mild to moderate, 1-2 indicates moderate to severe and 2-3 indicates very severe disability.

SF-36

SF-36 is a set of generic, coherent, and easily administered QoL measures which consists of 36 questions having vitality, physical function, pain etc., as components of questionnaire. It is widely used to cater the needs of researcher to understand the patients QoL. Achieving of higher score is indicating the patient is in "no disability" state. [3]

VAS

Visual Analog Scale (VAS) is widely popular instrument used in research to find out the intensity, frequency or QoL to sum up the patient's preference. Pain VAS score is characterizes as no pain, mild pain, moderate pain and severe pain. [4]

MOS - Sleep Measure

MOS – Sleep instrument is patient reported questionnaire having 12 questions related to actual hours of sleep, sleep disturbance, sleep initiation and maintenance. The score for each item was converted to a 0 - 100 range, with a higher score indicating more sleep problems. Scores from the 12 questions were averaged together to create seven scales. [4,5]

Objective

The objective of this review is to assess and evaluate the effectiveness and efficacy of the new biological DMARDs on the quality of life of rheumatoid arthritis patients through the use of health quality assessment tools such as HAQ score, SF-36, pain/ fatigue VAS and MOS-sleep scores.

Methodology

We searched for articles in Pubmed and included only randomized controlled trials testing the use of our drug of interest in rheumatoid arthritis. Only articles which have the QoL measures and complete data were included. Articles referring to data obtained from the same RCT are excluded to avoid duplicate results. The search terms used for each drug, the number of results obtained, and the number of articles used are listed in the appendix.

Discussion

Adalimumab

A total of eight studies were gathered with year ranging from 2004 to 2016 to evaluate the effectiveness of adalimumab on treating rheumatoid arthritis and the impact on the patient's QoL. The evaluation of adalimumab efficacy is based on the HAQ and VAS scores due to the common availability of data among the studies gathered. Some of the studies used SF-36 to assess the improvement in QoL, but data was not extracted due to insufficient data among other studies.

All the eight studies use the combination of adalimumab with methotrexate in treating rheumatoid arthritis, with the dose of adalimumab fixed at 40 mg. The total study period differs among some of the studies but ranges from as short as 12 weeks to as long as 104 weeks. Based on the improvement in HAQ scores in all studies, it can be concluded that adalimumab along with methotrexate combination is effective in treating RA patients and improves the QoL (**Table 1**). Seven out of eight studies (**Table 2**) have provided the data on VAS scores. According to the data obtained, the improvement was seen as soon as in within 12 weeks of taking the combination therapy, with progressive improvement until even 104 weeks. Both improvements in HAQ and VAS scores indicate that the combination therapy is efficacious in treating rheumatoid arthritis, and positively impacts the ability of a patient in

performing daily activities thus improving the quality of life. [5-12]

Anakinra

A total of four studies were gathered ranging from the year 2002 to 2016 to evaluate the efficacy and effectiveness of anakinra in the treatment of RA, improving the QoL of patients. Only four studies [13-16] were gathered due to the lack of studies performed on this particular topic of interest (**Table 3**). The evaluation is based on HAQ and VAS scores as other assessment on the QoL was not available in certain studies. Three out of four studies have a total study period of 24 weeks, while one study has a total study period of 104 weeks.

All of the studies showed significant improvement based on the HAQ and VAS scores, and the scores improved gradually as time passes by which is clearly shown in the study by Scott et al. [16] However, pain VAS score was unavailable. Regarding the therapy given either in monotherapy or in combination with methotrexate, it is observed that anakinra monotherapy showed far better improvement in terms of HAQ and VAS scores, but this information should not be 100% relied on as the particular study was conducted back in 2002, and only this one study uses anakinra monotherapy. Improvements in both monotherapy and combination therapy based on the scores clearly indicate that anakinra is effective in treating RA and improving the QoL of patients (**Table 4**).

Infliximab

Different therapies were initiated in these three studies (**Table 5**). [17-19] Goekoop-ruiterman Y.P.M et. al had a patient on dual therapy of infliximab and methotrexate. [17] Patients in Dae Hyun Yoo et. al study received CT-P13, which is a compound that is biosimilar to infliximab at week 14, 30 and 54. The result of the study showed mean D-HAQ score after 1 year were 0.5 in those receiving methotrexate and infliximab. The mean HAQ score difference was found to be 0.59 at week 14 and 0.6 at both week 30 and 54 respectively. [18] There are 109 out of 210 working-age patients used infliximab monotherapy in Jonas K. Eriksson et al study. The mean of work loss days was also assessed before and after the therapy. There was 25% improvement in HAQ score after 2 years of follow up and decrease of mean work loss days reported over 7 years after randomization. [19]

Rituximab

There are four studies evaluate patient's quality of life using health assessment questionnaire (HAQ). These studies are gathered from the year 2006 until the year 2016 with duration of treatment ranging from over 6 months to 1 year (**Table 6**). The patient is either found to be unresponsive to one or more of the anti-tumor necrosis factors or unrelieved with methotrexate in these three studies, so rituximab is added as an adjuvant therapy to give synergism effect. Both Stanley B Cohen et al [20] and Keystone et al. studies [21] showed 18 rituximab treated patient (6%) had a score of zero of HAQ-DI at week 24. The regimen given to active RA patients in William Rigby et al study were either 500 mg or 1000 mg rituximab. Patients on combination therapy of methotrexate and rituximab in this study showed ≥50% improvement of HAQ DI and the effect is extended up to 1 year. [22] Patients in Laure Gossec et .al study received 1000 mg rituximab twice a day for 2 weeks and were followed over 6 months, rituximab efficacy (HAQ-DI) plateau was reached at week 12. [23] In summary, rituximab-receiving patients exhibited statistically significant improvement in their level of disability and QoL. This may be due to the rapid and sustainable therapeutic effect of rituximab, which helps in improving physical function of RA patients.

Golimumab

2 studies have displayed Golimumab (GLM) monotherapy as a clinically meaningful improvement from the baseline of HAQ-DI scores. [28,29] Both studies have administered 50 mg GLM and 100 mg GLM subcutaneously in two separate groups of patients. These studies have shown similar results, which is that 100 mg GLM shows better improvement from baseline scores. Thus, the higher dose for subcutaneous administration of GLM monotherapy shows a higher improvement from baseline scores.

The remaining eight studies have shown the treatment of GLM with MTX at a different dose of subcutaneous GLM, which is 50 mg and 100mg in two separate groups of patients, except the studies done by Michael E.W. et al [26], Bernard Combe et al [27], Zhanguo Li et al [30] and Joel Kremer et al. [32] However, these studies with two different dose of subcutaneous GLM with MTX do not show much difference in the improvement from baseline score. The

studies done by Bernard Combe et al [27] and Zhanguo Li et al [30] uses 50 mg GLM administered subcutaneously, show clinically significant improvement from baseline scores. Out of those 8 studies, one study, done by Joel Kremer et al [32] in 2010, involved both GLM monotherapy and GLM together with MTX in two separate groups of patients. GLM is administered intravenously. This study has shown that the latter shows a significant improvement when compared to the former. There is an overall clinically significant improvement from baseline score in both treatment arms (**Table 7**).

In short, these 10 studies [24-33], done from the year 2009 to the year 2015, with the study duration ranging from 14 weeks to 156 weeks, these studies have shown the effectiveness of golimumab (GLM) by its significant improvement HAQ-DI score, which is used to assess the rheumatoid arthritis (RA) patient's quality of life (QoL).

Abatacept

There are 8 studies using HAQ-DI to assess the clinically significant improvement in the treatment of abatacept (ABA) with MTX (**Table 8**). 5 out of 8 studies administered ABA intravenously. The respective improvement from baseline scores for these studies done by R. Westhovens et al [35] in 2009 and 2006 [40], M. C. Genovese et al [36] and Alvin F. Wells et al [37] are 0.96, 0.5, 0.70, 1.0 while the study by Joel M. Kremer et al [41] shows 42.3% improvement from baseline scores.

Two studies done by M.C. Genovese et al [36, 42] and Jeffrey Kaine et al [38] have administered ABA subcutaneously, displaying 0.69 and 0.86 improvements from baseline score respectively. Overall, administration of abatacept through intravenous and subcutaneous route show clinically significant improvement from baseline scores.

5 studies have access the treatment of ABA with MTX by using VAS scores (**Table 9**). Studies done by Michael E Weinblatt et al [34], M.C. Genovese et al [36] in 2011 and Joel M. Kremer et al [41] have shown 50%, 44.9% and 44.9% improvement from baseline scores in patients administered with abatacept intravenously. A study done by M.C. Genovese [42] in 2007, involved patients administered with abatacept intravenously, improved by 37.2 from baseline score. The study was done by M.C. Genovese et al [36] in 2011 also administered abatacept subcutaneously and improved by 49.1% from baseline scores. Overall, all these studies show clinically significant improvement from baseline scores.

4 studies did not show clinically significant improvement in mental component score (MCS) (**Table 11**). However, studies were done by M.C. Genovese et al [43] in 2012, Paul Emery et al [44] in 2006 and R. Westhovens et al [40] in 2006 showed clinically significant improvement in physical component score (PCS). All these studies administered ABA intravenously to the patients. Overall, ABA administered intravenously have clinically significant improvement in PCS (**Table 10**).

2 studies have shown clinically significant improvement by using the tool of Medical Outcome Study Sleep questionnaire (MOS-Sleep). The former study shows an improvement score of 7.6 after the treatment of ABA + DMARDs. The latter study, done by Wells G.39 in 2010 involved treatment of ABA with DMARDs and treatment of ABA with MTX in two different groups of patients. The former treatment shows an improvement score of 11.3 while the latter shows only 2.9. This study has also shown that is a reliable and small sensitivity to change study. Thus, according to these two studies, the treatment of ABA + DMARDs may be more effective than ABA + MTX 39,45 (**Table 12**).

In short, there are 12 studies [34-45] concerning about the impact of ABA in rheumatoid arthritis (RA) patient's quality of life, taken from the year 2005 to the year 2015 and the duration of these studies range from 6 months to 5 years. Overall, these studies have shown significant improvement in RA patient's quality of life after using ABA because the improvement score meets the clinically meaningful improvement score. However, ABA is not given as a monotherapy in all these studies, it's either given with one of the DMARDs or with MTX.

Etanercept

16 studies46-61 ranging from the year 1999 to 2016 were gathered to evaluate the effect of etanercept on health outcomes (**Table 13**). The study periods ranged from 16 weeks to 104 weeks. HAQ-DI was used across all studies to evaluate patient's physical function and thus we report our findings based on HAQ-DI scores for better comparison.

A total of 7 studies evaluated the use of etanercept in combination with methotrexate in patients who had active disease despite using methotrexate. All 7 studies demonstrated improvement in HAQ-DI score when etanercept was added to MTX. All studies provided etanercept 50 mg to their patients, either administered weekly or divided into 2 doses. At the end of the trials, all studies showed improvement of at least 0.22 units in their HAQ-DI score, which is defined as a clinically meaningful improvement. Yamanaka et al [61] had almost 80% of their patients having more than 0.3 units of improvement. The improvement demonstrated by combining MTX and etanercept may be due to several factors such as the efficacy of methotrexate alone was insufficient but not negligible, and there is a synergistic or additive effect between the two drugs as they have a different mechanism of action.

Apart from being used as in combination with methotrexate, etanercept also can be used as a single agent. 8 studies found that patients who took etanercept as a monotherapy showed improvement in HAQ-DI scores at the end of the study period. Kameda et al47 van der Heijde et al50, Combe et al [55], van Riel et al56, Moreland et al [57] (1999), and Takeuchi et al [59] only included patients who were etanercept naïve while this was not specifically mentioned by Kosinski et al [51], Genovese et al [52], and Moreland et al [57] (1999). While all studies demonstrated improvement in HAQ-DI scores, Genovese et al [52], Moreland et al [57] (1999), and Takeuchi et al59 also utilized a lower dose of etanercept per week in their studies. Based on the results of their studies, it can be seen that the improvement is larger when etanercept is given at 25 mg twice weekly instead of 10 mg twice weekly. This improvement was found to be statistically significant in Genovese et al [52] and Takeuchi et al [59] study but not Moreland et al [58]. This means that it is possible for patients to be started on etanercept as a single agent instead of a combination. However, in Kameda et al [47] and van der Heijde et al [50] study, they found the combination of etanercept and MTX to be more effective than etanercept as a single agent while van Riel et al [56] found that there is no difference between the two options.

Finally, there are 4 studies focused on administering etanercept and MTX as a combination to patients who are etanercept and MTX naïve. In those studies, positive impact on the HAQ-DI scores was also observed. This may indicate that new patients may be started immediately on combination therapy with a biologic instead of the conventional strategy of beginning with methotrexate either alone or in combination with other DMARDs.

Therefore, it can be clearly seen that etanercept is an effective agent in treating rheumatoid arthritis in terms of patients' QoL outcomes as a single agent or in combination with MTX.

Certolizumab

12 studies ranging from the year 2009 to 2017 were gathered to evaluate the improvement of certolizumab in patient-reported outcomes (**Table 14**). The study periods ranged from 12 weeks to 104 weeks. All the studies utilize the HAQ-DI to evaluate patient's physical function and thus we report our findings based on HAQ-DI scores for better comparison.

A total of 5 studies evaluated the use of certolizumab in combination with MTX in patients who have an inadequate response to MTX. Based on the results of all the 5 studies, it can be seen that the addition of certolizumab resulted in more than 0.22 units of clinically relavant improvement in the HAQ-DI score at the end of their study periods. Out of 5 studies, only Yamamoto et al [62] (J-RAPID), and Strand et al [65,64] in 2009 and 2011 compared the effects of administering different doses of certolizumab in combination with methotrexate. In 2009, Strand et al [65] found similar results when using certolizumab 200 mg or 400 mg every 2 weeks. However, in 2011 [64], Strand et al. found a slightly greater improvement in HAQ-DI score when using certolizumab 400 mg every 2 weeks, and this is also found in Yamamoto et al [62] (J-RAPID)'s study where the improvement increased as the dose of certolizumab used increases from 100 mg to 400 mg every 2 weeks. Nevertheless, all 3 studies found no significant difference between the doses.

Another 2 studies also evaluated the use of certolizumab and MTX combination in patients who are DMARDs naïve. Atsumi et al [72] found that only a small proportion of patients have a HAQ-DI score of ≤0.5 while Emery et al [73] found good improvement in the patients' HAQ-DI score at the end of the study. In Atsumi et al. [72] study, oral methotrexate was given at 8 mg/week initially and then increased up to 16

mg/week step wisely by week 8 and then maintained thereafter while in Emery et al [73] study, oral methotrexate was initiated at 10 mg/week and increased up to 25 mg/week step wisely by week 8 if tolerated, and maintained until the end.

Fleischmann et al [63] studied the use of certolizumab 400 mg as a monotherapy in patients who failed at least 1 DMARD previously. At the end of the study, improvement of at least 0.22 units was observed in the patients indicating that monotherapy with certolizumab 400 mg may be effective.

Finally, 4 studies looked into the combination of certolizumab with various DMARDs. Yamamoto et al [69] (HIKARI) studied the use of certolizumab 200mg in patients who are unable to use methotrexate. Weinblatt et al [70], Smolen et al 68(2015), and Schiff et al [67] looked into the combination of certolizumab with conventional DMARDs. Similar to the other studies mentioned previously, the patients managed with the addition of certolizumab had a clinically relevant improvement in their HAQ-DI scores at the end of their studies.

Therefore, we can see that certolizumab is another option for patients with rheumatoid arthritis whose disease are not well controlled with MTX or other DMARDs. The addition of certolizumab resulted in clinically relevant improvement in the patients' HAQ-DI scores.

Tocilizumab

6 studies [74-79] from the year 2011 to 2017 were gathered to evaluate the improvement to patient's QoL (**Table 15**). HAQ-DI was used to evaluate patient's QoL as this is the common availability questionnaire used in most of the studies. The statistically significant improvement is observed in physical function of HAQ – DI using 8 mg Tocilizumab than 4 mg Tocilizumab after 52 weeks. [74-79] Similar improvement was observed in HAQ-DI when tocilizumab was taken as monotherapy or combination with methotrexate.

The overall results demonstrated that, Tocilizumab improves the QoL of RA patient which is statistically significant leading to consider the drug as valuable option in the treatment.

Tofacitinib

6 studies from the year 2015 to 2017 were gathered to evaluate the improvement of the patient's QoL. HAQ-DI and SF36 questionnaires were used in most of the studies (**Table 16**). The improvement physical functioning was statistically significant at all months after completion of 5 mg Tofacitinib [12, 80-84]. The greatest improvement compared to baseline are at 6 and 24 months with the average of -0.715 reductions from baseline while the least improvement from baseline is at month 3 with the average of -0.558 reduction from baseline. Similar improvements are observed when tofacitinib was given as monotherapy and as a combination with methotrexate [12, 80]. In SF36, physical component summary scores recorded significant improvement for 5 mg Tofacitinib dose (**Table 17**). Changes from baseline at month 24 were sustained to month 3, 6 and 12. When comparison with tofacitinib monotherapy and in combination with methotrexate, similar effects were observed in SF36 (PCS). Numerical improvement in mental component scores was observed in 5 mg Tofacitinib with greatest improvement at month 6 and 2412, [81]. Hence, Tofacitinib is more effective when used in long durations compare to short duration. Many patients in tofacitinib treatment group reported clinically meaningful improvement in the quality of life than placebo-treated groups. Together, the findings in HAQ-DI, SF-36 (PCS) and SF-36 (MCS) reflect a wide-ranging beneficial effect of Tofacitinib treatment on physical function and patient's QoL. [12, 80-84]

CONCLUSION

Overall, HAQ-DI, SF-36, VAS and MOS-Sleep have showed significant improvement in quality of life of rheumatoid arthritis patients who takes the combination therapy of newer biological agents - adalimumab, infliximab, rituximab, anakinra, tofacitinib, tocilizumab, certolizumab, etanercept, abatacept, and golimumab plus conventional DMARDs or as biological agent monotherapy. Current analyses also demonstrated that these agents have rapid and sustainable clinical effects as they are able to produce statistically significant improvement in QoL, relief of symptoms as well as bodily function.

Table 1: Summary of articles using Adalimumab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)					
				Baseline	12 weeks	24 weeks	52 weeks	76 weeks	104 weeks
Keystone et. al. (2004) [5]	Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial	Adalimumab 40 mg + MTX	52 weeks	1.45 ± 0.63	-	-0.56 ± 0.52	-0.59 ± 0.57	-	-
Breedweld et. al. (2005) [6]	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, aggresive rheumatoid arthritis who not had previous methotrexate treatment	Adalimumab 40 mg + MTX	104 weeks	1.5 ± 0.6	-	-	-	-	-1.0 ± 0.7
Bejarano et. al. (2008) [7]	Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis.	Adalimumab + MTX	52 weeks	1.3 ± 0.6	-	-	-0.7 ± 0.6	-	-
Chen et. al. (2009) [8]	Randomized, Double-blind, Placebo-controlled, Comparative Study of Human Anti-TNF Antibody Adalimumab in Combination with Methotrexate and Methotrexate Alone in Taiwanese Patients with Active Rheumatoid Arthritis	Adalimumab 40 mg + MTX	12 weeks	1.7 (1.5-1.9) [95% CI]	1.1 (0.8-1.4) [95% CI]	-	-	-	-
Strand et. al. (2012) [9]	Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study.	Adalimumab 40 mg + MTX	104 weeks	1.5 ± 0.6	0.7 ± 0.5	0.6 ± 0.5	0.5 ± 0.5	0.4 ± 0.5	0.3 ± 0.5
Heimans et. al. (2013) [10]	Health-related quality of life and functional ability in patients with early arthritis during remission steered treatment: results of the IMPROVED study.	Adalimumab 40 mg + MTX 25 mg	52 weeks	1.4 ± 0.65	-	-	0.81 ± 0.64	-	-
Smolen et. al. (2014) [11]	Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial	Adalimumab 40 mg + MTX	24 weeks	1.4 ± 0.7	-	0.4 ± 0.5	-	-	-
Strand et. al. (2016) [12]	Tofacitinib or adalimumab versus placebo: patientreported outcomes from a phase 3 study of active rheumatoid arthritis	Adalimumab 40 mg + MTX	12 weeks	1.50 ± 0.58	-0.50 ± 0.04	-	-	-	-

Table 2: Summary of articles using Adalimumab in the treatment along with Pain VAS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	Pain VAS (mm) (VAS; 0, no pain and 100, severe pain)					
				Baseline	12 weeks	24 weeks	52 weeks	76 weeks	104 weeks
Keystone et. al. (2004) [5]	Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial	Adalimumab 40 mg + MTX	52 weeks	55.9 ± 20.4	-	-28.2 ± 25.8	-29.4 ± 26.4	-	-
Breedweld et. al. (2005) [6]	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, aggresive rheumatoid arthritis who not had previous methotrexate treatment	Adalimumab 40 mg + MTX	104 weeks	62.5 ± 21.3	-	-	-	-	≥ 50% improvement from baseline
Chen et. al. (2009) [8]	Randomized, Double-blind, Placebo-controlled, Comparative Study of Human Anti-TNF Antibody Adalimumab in Combination with Methotrexate and Methotrexate Alone in Taiwanese Patients with Active Rheumatoid Arthritis	Adalimumab 40 mg + MTX	12 weeks	66.5 (60.8-72.1) [95% CI]	48.1 (40.9-55.4) [95% CI]	-	-	-	-
Strand et. al. (2012) [9]	Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study.	Adalimumab 40 mg + MTX	104 weeks	62.5 ± 21.3	23.2 ± 16.5	20.9 ± 16.5	16.8 ± 15.7	13.1 ± 15.0	9.6 ± 14.9
Heimans et. al. (2013) [10]	Health-related quality of life and functional ability in patients with early arthritis during remission steered treatment: results of the IMPROVED study.	Adalimumab 40 mg + MTX 25 mg	52 weeks	61 ± 20	-	-	31 ± 25	-	-
Smolen et. al. (2014) [11]	Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial	Adalimumab 40 mg + MTX	24 weeks	56.7 ± 23.0	-	8.9 ± 10.9	-	-	-
Strand et. al. (2016) [12]	Tofacitinib or adalimumab versus placebo: patientreported outcomes from a phase 3 study of active rheumatoid arthritis	Adalimumab 40 mg + MTX	12 weeks	56.29 ± 21.97	-22.49 ± 1.62	-	-	-	-

Anakinra

Table 3: Summary of articles using Anakinra in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)				
				Baseline	12 weeks	24 weeks	52 weeks	104 weeks
Nuki et. al. (2002) [13]	Long-term safety and maintenance of clinical improvement following treatment with anakinra(recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial.	Anakinra	24 weeks	1.5 ± 0.6	-	-0.26 ± 0.05	-	-
Cohen et. al. (2002) [14]	Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial.	Anakinra 2 mg/kg + MTX	24 weeks	1.3 ± 0.6	-0.39	-.0.51	-	-
Cohen et. al. (2004) [15]	A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate.	Anakinra 100 mg + MTX	24 weeks	1.4 (0.6)	-	-.0.29 ± 0.03	-	-
Scott et. al. (2016) [16]	A randomised trial evaluating anakinra in early active rheumatoid arthritis	Anakinra 100 mg + MTX	104 weeks	1.49 (0.71)	-	-	0.12 (-0.11-0.36) [95% CI]	0.28 (0.04-0.52) [95% CI]

Table 4: Summary of articles using Anakinra in the treatment along with Pain VAS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	Pain VAS (mm) (VAS; 0, no pain and 100, severe pain)		
				Baseline	12 weeks	24 weeks
Nuki et. al. (2002) [13]	Long-term safety and maintenance of clinical improvement following treatment with anakinra(recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial.	Anakinra	24 weeks	60 ± 17	-	-9 ± 3
Cohen et. al. (2002) [14]	Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial.	Anakinra 2 mg/kg + MTX	24 weeks	54.6 ± 21.4	-19.34	-22.78
Cohen et. al. (2004) [15]	A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate.	Anakinra 100 mg + MTX	24 weeks	59.2 ± 21.6	-	-19.0 ± 1.7

Infliximab

Table 5: Summary of articles using Infliximab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)						
				Baseline	12 weeks	24 weeks	30 weeks	36 weeks	52 weeks	104 weeks
Goekoop-ruiterman Y.P et al. (2005) [17]	Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial	Infliximab	52 weeks	1.4 ± 0.7	0.6 ± 0.6	0.5 ± 0.5	-	0.5 ± 0.6	0.5 ± 0.5	-
Dae Hyun Yoo (2015) [18]	A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study	Infliximab	54 weeks	1.61 ± 0.56	1.02 ± 0.62	-	1.01 0.64	-	0.99 ± 0.61	-
Jonas K. Eriksson et al. (2016) [19]	Infliximab Versus Conventional Combination Treatment and Seven-Year Work Loss in Early Rheumatoid Arthritis: Results of a Randomized Swedish Trial	Infliximab	50 weeks	1.2 ± 0.6	-	-	-	-	-	0.9 ± 0.5

Table 6: Summary of articles using Rituximab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)			
				Baseline	12 weeks	24 weeks	52 weeks
Stanley B Cohen et al. (2006) [20]	Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks	Rituximab + MTX	24 weeks	1.9 ± 0.6	-	-0.4 ± 0.6	-
Keystone et al. (2008) [21]	Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti–tumor necrosis factor therapy	Rituximab + MTX	24 weeks	1.86 ± 0.58	-	-0.44 ± 0.60	-
William Rigby et al. (2011) [22]	Effect of rituximab on physical function and quality of life in patients with rheumatoid arthritis previously untreated with methotrexate	RTX + 500 mg MTX RTX + 1000 mg MTX	52 weeks	1.77 ± 0.70 1.73 ± 0.66	- -	- -	-0.905 -0.916

Laure Gossec et .al (2015) [23]	Improvement in patient-reported outcomes after rituximab in rheumatoid arthritis patients: An open-label assessment of 175 patients	Rituximab	24 weeks	1.8 ± 0.6	-0.68 (-0.54 to -0.82) [95% CI]	-0.62 (-0.50 to -0.75) [95% CI]	-

Table 7: Summary of articles using Golimumab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)					
				Baseline	14 weeks	24 weeks	48 weeks	52 weeks	156 weeks
Yoshiya Tanaka et al (2011) [24]	Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study	50 mg GLM + MTX	24 weeks	1.0 ± 0.61	-	-0.33 ± 0.42	-	-	-
		100 mg GLM + MTX		0.9 ± 0.59	-	-0.45 ± 0.43	-	-	-
Yoshiya Tanaka et al (2015) [25]	Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial	50 mg GLM + MTX	156 weeks	0.9 ± 0.60	-	-	-	-	-0.75 ± 0.53
		100 mg GLM + MTX		0.9 ± 0.60	-	-	-	-	-0.71 ± 0.52
Michael E.W et al. (2014) [26]	Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial	MTX + IV GLM 2 mg/kg	14 weeks	1.6 ± 0.67	-0.50 ± 0.58	-	-	-	-
Bernard Combe et al. (2013) [27]	Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study	SC 50 mg GLM	24 weeks	1.44	-	-0.56	-	-	-
Tsutomu Takeuch et al. (2012) [28]	Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks	50 mg GLM	24 weeks	1.1 ± 0.6	-	-0.23 (0.13 to 0.33) [95% CI]	-	-	-
		100 mg GLM		1.0 ± 0.6	-	-0.33 (0.23 to 0.43) [95% CI]	-	-	-
E C Keystone et al. (2009) [29]	Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study	50 mg GLM	24 weeks	1.375 (0.875 to 1.875) [95% CI]	-	−0.38 (−0.75 to −0.13) [95% CI]	-	-	-
		100 mg GLM		1.375 (0.875 to 1.875) [95% CI]	-	−0.38 (−0.63 to −0.13) [95% CI]	-	-	-

Zhanguo Li et al. (2015) [30]	Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy	50mg GLM + MTX	52 weeks	1.3 ± 0.7	-	-	-	-0.40 ± 0.62	-
Paul Emery et al. (2013) [31]	Golimumab, a Human Anti–Tumor Necrosis Factor Monoclonal Antibody, Injected Subcutaneously Every 4 Weeks in Patients With Active Rheumatoid Arthritis Who Had Never Taken Methotrexate: 1-Year and 2-Year Clinical, Radiologic, and Physical Function Findings of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study	50mg GLM + MTX 100mg GLM + MTX	52 weeks	1.5 ± 0.7 1.5 ± 0.6	- -	- -	- -	0.66 ± 0.68 0.75 ± 0.67	- -
Joel Kremer et al. (2010) [32]	Golimumab, a New Human Anti–Tumor Necrosis Factor Alpha Antibody, Administered Intravenously in Patients With Active Rheumatoid Arthritis	GLM	48 weeks	1.5 ± 1.5)	-	-	14.4% ± 25.0%	-	-
Josef S Smolen et al. (2009) [33]	Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial	50 mg GLM 100 mg GLM	24 weeks	1·6 (1·1–2·0) [95% CI] 1·5 (1·0–2·0) [95% CI]	- -	1·4 (0·8 to 1·8) [95% CI] 1·1 (0·6 to 1·8) [95% CI]	- -	- -	- -

Table 8: Summary of articles using Abatacept in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)			
				Baseline	6 months	8 months	12 months
Michael E Weinblatt et al. (2013) [34]	Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study	SC ABA + MTX	12 months	1.5 ± 0.7	-	-	−0.60 ± 0.04
R Westhovens et al. (2009) [35]	Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors	ABA 10 mg/kg + MTX	12 months	1.7 ± 0.7	-	-	−0.96 ± 0.04
M C Genovese et al. (2011) [36]	Subcutaneous Abatacept vErsus Intravenous Abatacept: A Phase IIIb Noninferiority Study in Patients With an Inadequate Response to Methotrexate	SC ABA 125mg IV ABA 10 mg/kg	6 months	1.7 ± 0.7 1.7 ± 0.7	−0.69 ± 0.02 −0.70 ± 0.02	- -	- -
Alvin F. Wells et al. (2011) [37]	Abatacept Plus Methotrexate Provides Incremental Clinical Benefits Versus Methotrexate Alone in Methotrexate-naive Patients with Early Rheumatoid Arthritis Who Achieve Radiographic Nonprogression	ABA 10 mg/kg + MTX	12 months	1.6 ± 0.7	-	-	−1.0 ± 0.8

Jeffrey Kaine et al. (2012) [38]	Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study)	SC ABA 125mg	8 months	1.4 ± 0.7	-	-0.86 (-1.04, -0.67) [95% CI]	-
Wells G et al. (2008) [39]	Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis.	ABA + DMARDs	6 months	1.8 ± 0.6	-0.33 (-0.44 to -0.22) [95% CI]	-	-
R Westhovens et al. (2006) [40]	Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial	ABA 10 mg/kg + DMARDs	6 months	1.8 ± 0.6	−0.5 ± 0.6	-	-
Joel M. Kremer et al. (2005) [41]	Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: Twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial	ABA 10 mg/kg + MTX	12 months	1.0 ± 0.5	-	-	42.3%

Table 9: Summary of articles using Abatacept in the treatment along with Pain VAS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	Pain VAS (mm) (VAS; 0, no pain and 100, severe pain)			
				Baseline	6 months	12 months	24 months
Michael E Weinblatt et al. (2013) [34]	Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study	SC ABA + MTX	12 months	63.1 ± 22.3	-	50%	-
M C Genovese et al. (2011) [36]	Subcutaneous Abatacept vErsus Intravenous Abatacept: A Phase IIIb Noninferiority Study in Patients With an Inadequate Response to Methotrexate	SC ABA 125mg IV ABA 10 mg/kg	6 months	68 ± 20.0 66.9 ± 20.5	49.1 ± 1.74% 44.9 ± 1.77%	- -	- -
Wells G et al. (2008) [39]	Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis.	ABA + DMARDs	6 months	70.8 ± 19.8	-20.0 (-26.2 to -13.7) [95% CI]	-	-
Joel M. Kremer et al. (2005) [41]	Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: Twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial	ABA 10 mg/kg + MTX	12 months	62.6 ± 20.6	-	62.6 ± 20.6	-

M C Genovese et al. (2007) [42]	Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy	ABA + DMARDs	24 months	70.6 ± 19.4	-	-	-37.2 ± 2.4

Table 10: Summary of articles using Abatacept in the treatment along with PCS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	PCS (Scale: 0 to 100, 100 being the best)			
				Baseline	6 months	12 months	60 months
Wells G et al. (2008) [39]	Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis.	ABA + DMARDs	6 months	27.5 ± 6.9	-5.5 (3.6 to 7.4) [95% CI]	-	-
M C Genovese et al. (2012) [43]	Long term safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy.	ABA + DMARDs	60 months	27.7 ± 6.8	-	-	-7.46 (6.11 - 8.81) [95% CI]
Paul Emery et al. (2006) [44]	Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life.	ABA 10mg/kg + MTX	52 weeks	30.7 ± 8.4	-	-8 ± 0.8	-

Table 11: Summary of articles using Abatacept in the treatment along with MCS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	MCS (Scale: 0 to 100, 100 being the best)			
				Baseline	6 months	12 months	60 months
Wells G et al. (2008) [39]	Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis.	ABA + DMARDs	6 months	41.3 ± 12.4	-3.7 (1.3 to 6.1) [95% CI]	-	-
R Westhovens (2006) [40]	Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical	ABA 10 mg/kg + DMARDs	6 months	41.2 ± 12.4	-5.4 ± 11.7	-	-
M C Genovese et al. (2012) [43]	Long term safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy.	ABA + DMARDs	60 months	41.4 ± 12.6	-	-	-5.83 (4.18–7.47) [95% CI]
Paul Emery et al. (2006) [44]	Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life.	ABA 10mg/kg + MTX	52 weeks	45.6 ± 12.6	-	-5.7 (0.9) [95% CI]	-

Table 12: Summary of articles using Abatacept in the treatment along with MOS measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	MOS (Scale: 0 to 100, 100 being the worst)	
				Baseline	6 months
Wells G et al. (2008) [39]	Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis.	ABA + DMARDs	6 months	41.3 ± 12.4	-3.7 (1.3 to 6.1) [95% CI]
Wells G et al. (2010) [45]	Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale.	ABA + DMARDs	6 months	50.0 ± 26.5	-11.3
		ABA + MTX		46.4 ± 27.2	-2.9

Table 13: Summary of articles using Etanercept in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)	
				Baseline	End of Study Period
O'Dell et al. (2013) [46]	Therapies for Active Rheumatoid Arthritis after Methotrexate Failure	ETN 50mg weekly (add on) + MTX	48 weeks	1.46 ± 0.78 (SD)	0.73 ± 0.79
Kameda et al. (2011) [47]	Continuation of Methotrexate Resulted in Better Clinical and Radiographic Outcomes Than Discontinuation upon Starting Etanercept in Patients with Rheumatoid Arthritis: 52-week Results from the JESMR Study	ETN 25mg twice weekly	52 weeks	1.3 ± 0.8 (SD)	0.9 ± 0.7 (SD)
		ETN 25mg twice weekly (add on) + MTX		1.2 ± 0.7 (SD)	0.6 ± 0.6 (SD)
Bae et al. (2013) [48]	Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis.	ETN 25mg twice weekly (add on) + MTX	16 weeks	1.37 ± 0.68	0.69
Machado et al. (2014) [49]	Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region.	ETN 50mg weekly (add on) + MTX	24 weeks	1.6 ± 0.7 (SD)	0.7 ± < 0.1 (SE)
van der Heijde et al. (2006) [50]	Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial	ETN 25mg twice weekly	52 weeks	1.7 ± 0.7 (SD)	1
		ETN 25mg twice weekly + MTX		1.8 ± 0.6 (SD)	0.8
Kosinski et al. (2002) [51]	Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response.	ETN 25mg twice weekly	52 weeks	N/A	-0.73 ± 0.05 (SD)
Genovese et al. (2002) [52]	Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.	ETN 10mg twice weekly	104 weeks	1.4-1.5	Approx. 43% of patients have ≥0.5 units of improvement
		ETN 25mg twice weekly		1.4-1.5	Approx. 55% of patients have ≥0.5 units of improvement
Weinblatt et al. (1999) [53]	A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.	ETN 25mg twice weekly (add on) + MTX	24 weeks	1.5	0.8
Emery et al. (2008) [54]	Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial	ETN 50mg weekly + MTX	52 weeks	1.7 ± 0.7 (SD)	0.7
Combe et al. (2009) [55]	Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study	ETN 25mg twice weekly	104 weeks	1.73	1.12
van Riel et al. (2008) [56]	Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial	ETN 25mg twice weekly	16 weeks	N/A	-0.59 ± 0.69 (SD)
		ETN 25mg twice weekly (add on) + MTX		N/A	-0.59 ± 0.58 (SD)

Moreland et al. (1999) [57]	Etanercept Therapy in Rheumatoid Arthritis. A Randomized, Controlled Trial	ETN 10mg twice weekly	26 weeks	1.7	1.12
		ETN 25mg twice weekly		1.6	0.98
Moreland et al. (2012) [58]	A Randomized Comparative Effectiveness Study of Oral Triple Therapy versus Etanercept plus Methotrexate in Early, Aggressive Rheumatoid Arthritis	ETN 50mg weekly+ MTX	102 weeks	1.1 ± 0.4 (SD)	1.0 ± 0.3 (SD)
Takeuchi et al. (2013) [59]	A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis.	ETN 10mg twice weekly	52 weeks	1.2 ± 0.7 (SD)	0.6 (53.7% improvement)
		ETN 25mg twice weekly		1.1 ± 0.7 (SD)	0.5 (58.1% improvement)
Nam et al. (2014) [60]	A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial.	ETN 50mg weekly + MTX	52 weeks	1.01 ± 0.47 (SD)	0.61
Yamanaka et al. (2016) [61]	Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who initially had moderate disease activity-results from the ENCOURAGE study, a prospective, international, multicenter randomized study.	ETN 25mg twice weekly (add on) + MTX	52 weeks	0.8 ± 0.6	76.8% of 155 patients had score <0.5

Table 14: Summary of articles using Certolizumab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)	
				Baseline	End of Study Period
Yamamoto et al. (2014) [62]	Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial.	CZP 100mg (add on) +MTX	24 weeks	1.2 ± 0.7 (SD)	-0.43 ± 0.06 (SE)
		CZP 200mg (add on) +MTX		1.1 ± 0.7 (SD)	-0.55 ± 0.05 (SE)
		CZP 400mg (add on) +MTX		1.1 ± 0.6 (SD)	-0.57 ± 0.05 (SE)
Fleischmann et al. (2009) [63]	Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study.	CZP 400mg	24 weeks	1.4 ± 0.63 (SD)	-0.36
Strand et al. (2011) [64]	Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial.	CZP 200mg (add on) + MTX	24 weeks	1.6 ± 0.6 (SD)	-0.5
		CZP 400mg (add on) + MTX		1.6 ± 0.6 (SD)	-0.5
Strand et al. (2009) [65]	Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial.	CZP 200mg (add on) + MTX	52 weeks	1.7 ± 0.6 (SD)	-0.57
		CZP 400mg (add on) + MTX		1.7 ± 0.6 (SD)	-0.61

Choy et al. (2012) [66]	Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX	CZP 400mg (add on) + MTX	24 weeks	1.4 ± 0.6 (SD)	-0.32
Schiff et al. (2014) [67]	Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase.	CZP 200mg (add on) + stable DMARDS	12 weeks	1.5	66.7% (n=18) achieved ≥0.3 change from baseline.
Smolen et al. (2016) [68]	Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study.	CZP 200mg (add on) + MTX	104 weeks	1.5 ± 0.6 (SD)	-0.62
Yamamoto et al. (2014) [69]	Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial.	CZP 200mg (add on)	24 weeks	1.21 ± 0.67 (SD)	-0.48 ± 0.05 (SE)
Weinblatt et al. (2012) [70]	Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study.	CZP 200mg (add on)	12 weeks	1.5 ± 0.6 (SD)	-0.43 ± 0.02 (SE)
Smolen et al. (2015) [71]	Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial.	CZP 200mg (add on) + DMARDS	24 weeks	1.11 ± 0.62 (SD)	-0.25 ± 0.46 (SD)
Atsumi et al. (2016) [72]	The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression.	CZP 200mg + MTX	52 weeks	1.0 ± 0.6 (SD)	43 had ≤0.5 44 had >0.5–≤1.0 71 had >1.0
Emery et al. (2017) [73]	Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study	CZP 200mg + MTX	52 weeks	1.6 ± 0.6 (SD)	-0.997

Table 15: Summary of articles using Tocilizumab in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)		
				Baseline	12 weeks	52 weeks
Strand V et al. (2012) [74]	Improvement in health related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study.	4 mg TCZ 8 mg TCZ	24 weeks	1.7 ± 0.6 1.7 ± 0.6	-0.31 -0.39	 -
Lremer JL et al. (2011) [75]	Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year	MTX+ 4 mg TCZ MTX +8 mg TCZ	52 weeks	1.5 ± 0.6 1.5 ± 0.6	 -	-0.6 -0.5

Burnmester GR et al. (2015) [76]	Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial	MTX + 4 mg TCZ MTX+ 8 mg TCZ	52 weeks	1.62 ± 0.662 1.50 ± 0.625	-0.1 -0.11	-0.17 -0.17
Fleishmann RM et al. (2013) [77]	Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results.	MTX + 4 mg TCZ MTX +8 mg TCZ	52 weeks	1.73 ± 0.4 1.72 ± 0.6	- -	-0.95 -0.86
Kihara M et al. (2017) [78]	Use and effectiveness of tocilizumab among patients with rheumatoid arthritis: an observational study from the British Society for Rheumatology Biologics Register for rheumatoid arthritis	4 mg TCZ	24 weeks	1.6 ± 1.1	-0.3	-
Hammoudeh M et al. (2015) [79]	Safety, Tolerability, and Efficacy of Tocilizumab in Rheumatoid Arthritis: An Open-Label Phase 4 Study in Patients from the Middle East	4 mg TCZ	24 weeks	1.6 ± 0.6	-0.22 (0.5)	-

Table 16: Summary of articles using Tofacitinib in the treatment along with HAQ – DI measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	HAQ-DI (HAQ; 0, without difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do so)				
				Baseline	3 months	6 months	12 months	24 months
Strand V et al. (2016) [80]	Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial.	5 mg Tofacitinib	24 months	1.54 ± 0.64	−0.76 ± 0.03	−0.84 ± 0.03	−0.88 ± 0.03	−0.91 ± 0.03
Strand V et al. (2015) [81]	Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial.	5 mg Tofacitinib + MTX	3 months	1.60 ± 0.66	-0.43 ± 0.04	-	-	-
G.V Wallenstein et al. (2016) [82]	Effects of the oral Janus kinase inhibitor tofacitinib on patient-reported outcomes in patients with active rheumatoid arthritis: results of two Phase 2 randomised controlled trials	5 mg Tofacitinib	24 months	1.4 ± 0.7	-	-	-0.5 ± 0.3	-0.52 ± 0.3
Strand V et al. (2016) [12]	Tofacitinib or adalimumab versus placebo: patientreported outcomes from a phase 3 study of active rheumatoid arthritis	5 mg Tofacitinib + MTX	3 months	1.50 ± 0.64	-0.54 ±0.04	-	-	-
Strand V et al. (2015) [83]	Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs	5 mg Tofacitinib	6 months	1.53 ± 0.66	−0.50 ± 0.03	−0.59 ± 0.07	-	-
Strand V et al. (2017) [84]	Tofacitinib in Combination With Conventional Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis: Patient-Reported Outcomes From a Phase III Randomized Controlled Trial	5 mg Tofacitinib	3 months	1.44 ± 0.69	-0.56 ± 0.03	-	-	-

Table 17: Summary of articles using Tofacitinib in the treatment along with SF-36 measurement

Author and Year	Title	Treatment/ Intervention	Total Study Period	SF 36 (PCS)					SF 36 (MCS)				
				Baseline	3 months	6 months	12 months	24 months	Baseline	3 months	6 months	12 months	24 months
Strand V et al. (2016) [80]	Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial.	5 mg Tofacitinib	24 months	32.82 ± 7.25	40.47 ± 12.05	9.74 ± 0.44	10.34 ± 0.45	11.14 ± 0.46	40.47 ± 2.05	6.19 ± 0.51	6.43 ± 0.52	6.27 ± 0.53	6.20 ± 0.55
Strand V et al. (2015) [81]	Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial.	5 mg Tofacitinib + MTX	3 months	30.72 ± 9.29	42.82 ± 12.69	-	-	-	42.82 ± 12.69	3.52 ± 0.92	-	-	-
G.V Wallenstein et al. (2016) [82]	Effects of the oral Janus kinase inhibitor tofacitinib on patient-reported outcomes in patients with active rheumatoid arthritis: results of two Phase 2 randomised controlled trials	5 mg Tofacitinib	24 months	30.2 ± 6.8	47.69 ± 13.4	-	5.5 ± 0.3	6.9 ± 0.5	47.69 ± 13.4	-	-	3.2 ± 0.45	4.1 ± 0.56
Strand V et al. (2016) [12]	Tofacitinib or adalimumab versus placebo: patient reported outcomes from a phase 3 study of active rheumatoid	5 mg Tofacitinib + MTX	3 months	33.14 ± 7.74	39.78 ± 11.69	-	-	-	39.78 ± 11.69	3.16 ± 0.66	-	-	-

	arthritis												
Strand V et al. (2015) [83]	Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs	5 mg Tofacitinib	6 months	31.23 ± 8.03	41.36 ± 11.68	5.18 ± 1.09	-	-	41.36 ± 11.68	4.11 ± 0.61	3.83 ± 1.23	-	-
Strand V et al. (2017) [84]	Tofacitinib in Combination With Conventional Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis: Patient-Reported Outcomes From a Phase III Randomized Controlled Trial	5 mg Tofacitinib	3 months	32.4 ± 7.8	40.9 ± 12.6	-	-	-	40.9 ± 12.6	4.4 ± 0.5	-	-	-

REFERENCES

1. Smith H. Rheumatoid Arthritis [Internet]. Emedicine.medscape.com. 2017 [cited 31 July 2017]. Available from: http://emedicine.medscape.com/article/331715-overview
2. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003 Jun 9; 1:20.
3. 36-Item Short Form Survey (SF-36) | RAND [Internet]. Rand.org. [cited 31 July 2017]. Available from: https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html
4. Visual Analogue Scale - Physiopedia [Internet]. Physio-pedia.com. [cited 31 July 2017]. Available from: http://www.physio-pedia.com/Visual_Analogue_Scale
5. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11.
6. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. 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. 2006 Jan;54(1):26-37.
7. Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D, Gough A, Green M, McGonagle D, Adebajo A, Jarrett S, Doherty S, Hordon L, Melsom R, Unnebrink K, Kupper H, Emery P; Yorkshire Early Arthritis Register Consortium. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum. 2008 Oct 15;59(10):1467-74.
8. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, Lan JL. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc. 2009 Apr;108(4):310-9.
9. Strand V, Rentz AM, Cifaldi MA, Chen N, Roy S, Revicki D. Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. J Rheumatol. 2012 Jan;39(1):63-72.
10. Heimans L, Wevers-de Boer KV, Koudijs KK, Visser K, Goekoop-Ruiterman YP, Harbers JB, Steup-Beekman GM, Lard LR, Grillet BA, Huizinga TW, Allaart CF. Health-related quality of life and functional ability in patients with early arthritis during remission steered treatment: results of the IMPROVED study. Arthritis Res Ther. 2013 Oct 31;15(5):R173.
11. Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, Guérette B, Kupper H, Redden L, Arora V, Kavanaugh A. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomized controlled OPTIMA trial. Lancet. 2014 Jan 25;383(9914):321-32.
12. Strand V, van Vollenhoven RF, Lee EB, Fleischmann R, Zwillich SH, Gruben D, Koncz T, Wilkinson B, Wallenstein G. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology (Oxford). 2016 Jun;55(6):1031-41.
13. Nuki G, Bresnihan B, Bear MB, McCabe D; European Group Of Clinical Investigators. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46.
14. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, Kremer J, Bear MB, Rich WJ, McCabe D. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.
15. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, Hanrahan PS, Kraishi MM, Patel A, Sun G, Bear MB; 990145 Study Group. A multicentre, double-blind, randomized, placebo-controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8.
16. Scott IC, Ibrahim F, Simpson G, Kowalczyk A, White-Alao B, Hassell A, Plant M, Richards S, Walker D, Scott DL. A randomized trial evaluating anakinra in early active rheumatoid arthritis. Clin Exp Rheumatol. 2016 Jan-Feb;34(1):88-93.
17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC, Dijkmans BA. Clinical and radiographic outcomes of four different

treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2008 Feb;58(2 Suppl):S126-35.
18. Yoo DH, Racewicz A, Brzezicki J, Yatsyshyn R, Arteaga ET, Baranauskaite A, Abud-Mendoza C, Navarra S, Kadinov V, Sariego IG, Hong SS, Lee SY, Park W. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 2016 Apr 2;18:82.
19. Eriksson JK, Wallman JK, Miller H, Petersson IF, Ernestam S, Vivar N, van Vollenhoven RF, Neovius M. Infliximab Versus Conventional Combination Treatment and Seven-Year Work Loss in Early Rheumatoid Arthritis: Results of a Randomized Swedish Trial. Arthritis Care Res (Hoboken). 2016 Dec;68(12):1758-1766.
20. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006 Sep;54(9):2793-806.
21. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, Tak PP, Broder MS, Yu E, Cravets M, Magrini F, Jost F. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008 Jun 15;59(6):785-93.
22. Rigby W, Ferraccioli G, Greenwald M, Zazueta-Montiel B, Fleischmann R, Wassenberg S, Ogale S, Armstrong G, Jahreis A, Burke L, Mela C, Chen A. Effect of rituximab on physical function and quality of life in patients with rheumatoid arthritis previously untreated with methotrexate. Arthritis Care Res (Hoboken). 2011 May;63(5):711-20.
23. Gossec L, Danré A, Combe B, Le Loët X, Tebib J, Sibilia J, Mariette X, Dougados M. Improvement in patient-reported outcomes after rituximab in rheumatoid arthritis patients: An open-label assessment of 175 patients. Joint Bone Spine. 2015 Dec;82(6):451-4.
24. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, Miyasaka N, Koike T, Kanazawa M, Oba T, Yoshinari T, Baker D; GO-FORTH Study Group. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012 Jun;71(6):817-24.
25. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, Miyasaka N, Koike T, Baker D, Ishii Y, Yoshinari T; GO-FORTH study group. Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. Mod Rheumatol. 2016 Jul;26(4):481-90.
26. Weinblatt ME, Westhovens R, Mendelsohn AM, Kim L, Lo KH, Sheng S, Noonan L, Lu J, Xu Z, Leu J, Baker D, Bingham CO; GO-FURTHER investigators. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. Ann Rheum Dis. 2014 Dec;73(12):2152-9.
27. Combe B, Dasgupta B, Louw I, Pal S, Wollenhaupt J, Zerbini CA, Beaulieu AD, Schulze-Koops H, Durez P, Yao R, Vastesaeger N, Weng HH; GO-MORE Investigators. Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. Ann Rheum Dis. 2014 Aug;73(8):1477-86.
28. Takeuchi T, Harigai M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, Miyasaka N, Koike T, Kanazawa M, Oba T, Yoshinari T, Baker D; GO-MONO study group. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks. Ann Rheum Dis. 2013 Sep 1;72(9):1488-95.
29. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU; GO-FORWARD Study. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96.
30. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, Wu Z, Hsia EC. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. Int J Rheum Dis. 2016 Nov;19(11):1143-1156.
31. Emery P, Fleischmann RM, Doyle MK, Strusberg I, Durez P, Nash P, Amante E, Churchill M, Park W, Pons-Estel B, Xu W, Xu S, Wu Z, Hsia EC. Golimumab, a human anti–tumor necrosis factor monoclonal antibody, injected subcutaneously every 4 weeks in patients with active rheumatoid arthritis who had never taken methotrexate: 1-year and 2-year clinical, radiologic, and physical function findings of

a phase III, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Care Res (Hoboken). 2013 Nov;65(11):1732-42.
32. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, Han J, Taylor P. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2010 Apr;62(4):917-28.
33. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S, Hsia EC, Rahman MU; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21.
34. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, Maldonado M, Fleischmann R. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013 Jan;65(1):28-38.
35. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, Gomez-Reino J, Grassi W, Haraoui B, Shergy W, Park SH, Genant H, Peterfy C, Becker JC, Covucci A, Helfrick R, Bathon J. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009 Dec;68(12):1870-7.
36. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, Nash P, Simon-Campos JA, Porawska W, Box J, Legerton C 3rd, Nasonov E, Durez P, Aranda R, Pappu R, Delaet I, Teng J, Alten R. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 Oct;63(10):2854-64.
37. Wells AF, Westhovens R, Reed DM, Fanti L, Becker JC, Covucci A, Keystone EC. Abatacept plus methotrexate provides incremental clinical benefits versus methotrexate alone in methotrexate-naive patients with early rheumatoid arthritis who achieve radiographic nonprogression. J Rheumatol. 2011 Nov;38(11):2362-8.
38. Kaine J, Gladstein G, Strusberg I, Robles M, Louw I, Gujrathi S, Pappu R, Delaet I, Pans M, Ludivico C. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study). Ann Rheum Dis. 2012 Jan;71(1):38-44. doi: 10.1136/annrheumdis-2011-200344. Epub 2011 Sep 13.
39. Wells G, Li T, Maxwell L, Maclean R, Tugwell P. Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):260-5.
40. Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, Blaisdell B, Wallenstein GV, Aranda R, Sherrer Y. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 Oct;45(10):1238-46.
41. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, Steinfeld S, Tindall E, Becker JC, Li T, Nuamah IF, Aranda R, Moreland LW. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):2263-71. Erratum in: Arthritis Rheum. 2005 Oct;52(10):3321.
42. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, Li T, Schmidely N, Le Bars M, Dougados M. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):547-54.
43. Genovese MC, Schiff M, Luggen M, Le Bars M, Aranda R, Elegbe A, Dougados M. Long term safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol. 2012 Aug;39(8):1546-54.
44. Emery P, Kosinski M, Li T, Martin M, Williams GR, Becker JC, Blaisdell B, Ware JE Jr, Birbara C, Russell AS. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 Apr;33(4):681-9.
45. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis. 2010 Oct;69(10):1768-73.
46. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, Lew RA, Cannella AC, Kunkel G, Phibbs CS, Anis AH, Leatherman S, Keystone E; CSP 551 RACAT Investigators. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013 Jul 25;369(4):307-18.
47. Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, Tsukano M, Kasama T, Shiozawa S, Tanaka Y, Yamanaka H, Takeuchi T.

Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol. 2011 Aug;38(8):1585-92.
48. Bae SC, Gun SC, Mok CC, Khandker R, Nab HW, Koenig AS, Vlahos B, Pedersen R, Singh A. Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. BMC Musculoskelet Disord. 2013 Jan 8;14:13.
49. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, Ferdousi T, Koenig AS, Kotak S, Vlahos B. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. J Clin Rheumatol. 2014 Jan;20(1):25-33.
50. Van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, Pedersen R, Freundlich B, Fatenejad S. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2006 Mar;65(3):328-34.
51. Kosinski M, Kujawski SC, Martin R, Wanke LA, Buatti MC, Ware JE Jr, Perfetto EM. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002 Mar;8(3):231-40.
52. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Cannon GW, Spencer-Green G, Finck BK. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002 Jun;46(6):1443-50.
53. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.
54. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS, Freundlich B. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008 Aug 2;372(9636):375-82.
55. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Khandker R, Singh A, Wajdula J, Fatenejad S; Etanercept European Investigators Network. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009 Jul;68(7):1146-52.
56. Van Riel PL, Freundlich B, MacPeek D, Pedersen R, Foehl JR, Singh A; ADORE Study Investigators. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. Ann Rheum Dis. 2008 Aug;67(8):1104-10.
57. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, Weinblatt ME. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
58. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, Bridges SL Jr, Zhang J, McVie T, Howard G, van der Heijde D, Cofield SS; 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. 2012 Sep;64(9):2824-35.
59. Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, Yuasa H, Vlahos B. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013 Jul;23(4):623-33.
60. Nam JL, Villeneuve E, Hensor EM, Wakefield RJ, Conaghan PG, Green MJ, Gough A, Quinn M, Reece R, Cox SR, Buch MH, van der Heijde DM, Emery P. A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. Ann Rheum Dis. 2014 Jun;73(6):1027-36.
61. Yamanaka H, Nagaoka S, Lee SK, Bae SC, Kasama T, Kobayashi H, Nishioka Y, Ueki Y, Seto Y, Nishinarita M, Tamura N, Kimura N, Saito K, Tomita T, Nawata Y, Suzuki S, Ishigatsubo Y, Munakata Y, Makino Y, Inoue E, Tanaka Y, Takeuchi T; ENCOURAGE study group. Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who initially had moderate disease activity-results from the ENCOURAGE study, a prospective, international, multicenter randomized study. Mod Rheumatol. 2016 Sep;26(5):651-61.
62. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Shoji T, Sakamaki Y, van der Heijde D, Miyasaka N, Koike T. Efficacy and safety of certolizumab pegol plus

methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014 Sep;24(5):715-24.
63. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11.
64. Strand V, Smolen JS, van Vollenhoven RF, Mease P, Burmester GR, Hiepe F, Khanna D, Nikaï E, Coteur G, Schiff M. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. Ann Rheum Dis. 2011 Jun;70(6):996-1002.
65. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, Combe B, Keystone EC, Kavanaugh A. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Res Ther. 2009;11(6):R170.
66. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, Davies O, Stahl HD, Alten R. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012 Jul;51(7):1226-34.
67. Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis. 2014 Dec;73(12):2174-7.
68. Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, van Vollenhoven R, Cioffi C, Ecoffet C, Gervitz L, Ionescu L, Peterson L, Fleischmann R. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet. 2016 Dec 3;388(10061):2763-2774.
69. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Iwai K, Sakamaki Y, van der Heijde D, Miyasaka N, Koike T. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol. 2014 Jul;24(4):552-60.
70. Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM, van Vollenhoven RF, Wollenhaupt J, Bingham CO 3rd, Duncan B, Goel N, Davies OR, Dougados M. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology (Oxford). 2012 Dec;51(12):2204-14.
71. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, Koetse W, Purcaru O, Bennett B, Burkhardt H. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Ann Rheum Dis. 2015 May;74(5):843-50.
72. Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Yasuda S, Yamanishi Y, Kita Y, Matsubara T, Iwamoto M, Shoji T, Okada T, van der Heijde D, Miyasaka N, Koike T. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016 Jan;75(1):75-83.
73. Emery P, Bingham CO 3rd, Burmester GR, Bykerk VP, Furst DE, Mariette X, van der Heijde D, van Vollenhoven R, Arendt C, Mountian I, Purcaru O, Tatla D, VanLunen B, Weinblatt ME. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. Ann Rheum Dis. 2017 Jan;76(1):96-104.
74. Strand V, Burmester G, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Rheumatology. 2012;51(10):1860-1869.
75. Kremer J, Blanco R, Brzosko M, Burgos-Vargas R, Halland A, Vernon E et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structu. Arthritis & Rheumatism. 2011;63(3):609-621.
76. Burmester G, Rigby W, van Vollenhoven R, Kay J, Rubbert-Roth A, Kelman A et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Annals of the Rheumatic Diseases. 2015;75(6):1081-1091.
77. FLEISCHMANN R, HALLAND A, BRZOSKO M, BURGOS-VARGAS R, MELA C, VERNON E et al. Tocilizumab Inhibits Structural Joint Damage and

Improves Physical Function in Patients with Rheumatoid Arthritis and Inadequate Responses to Methotrexate: LITHE Study 2-year Results. The Journal of Rheumatology. 2013;40(2):113-126.
78. Kihara M, Davies R, Kearsley-Fleet L, Watson K, Lunt M, Symmons D et al. Use and effectiveness of tocilizumab among patients with rheumatoid arthritis: an observational study from the British Society for Rheumatology Biologics Register for rheumatoid arthritis. Clinical Rheumatology. 2016;36(2):241-250.
79. Hammoudeh M, Al Awadhi A, Hasan E, Akhlaghi M, Ahmadzadeh A, Sadeghi Abdollahi B. Safety, Tolerability, and Efficacy of Tocilizumab in Rheumatoid Arthritis: An Open-Label Phase 4 Study in Patients from the Middle East. International Journal of Rheumatology. 2015;2015:1-7.
80. Strand V, Lee E, Fleischmann R, Alten R, Koncz T, Zwillich S et al. Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial. RMD Open. 2016;2(2):e000308.
81. Strand V, Burmester G, Zerbini C, Mebus C, Zwillich S, Gruben D et al. Tofacitinib With Methotrexate in Third-Line Treatment of Patients With Active Rheumatoid Arthritis: Patient-Reported Outcomes From a Phase III Trial. Arthritis Care & Research. 2015;67(4):475-483.
82. Wallenstein GV, Kanik KS, Wilkinson B, Cohen S, Cutolo M, Fleishmann R, Genovese MC, Gomez Reino J, Gruben D, Kremer J, Krishnaswami S, Lee EB, Pascual-Ramos V, Strand V, Zwillich S et al. Effects of the oral Janus kinase inhibitor tofacitinib on patient-reported outcomes in patients with active rheumatoid arthritis: results of two Phase 2 randomised controlled trials. Clinical and Experimental Rheumatology. 2016 May-Jun;34(3):430-42.
83. Strand V, Kremer J, Wallenstein G, Kanik K, Connell C, Gruben D et al. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. Arthritis Research & Therapy. 2015;17(1).
84. Strand V, Kremer J, Gruben D, Krishnaswami S, Zwillich S, Wallenstein G. Tofacitinib in Combination With Conventional Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis: Patient-Reported Outcomes From a Phase III Randomized Controlled Trial. Arthritis Care & Research. 2017;69(4):592-598.