Adalimumab: 8 years of experience in rheumatoid arthritis

Rheumatoid arthritis is the most common autoimmune inflammatory arthritis. TNF-α has a pivotal role in its pathogenesis. Adalimumab was the first fully human antibody against TNF-α to be approved for active rheumatoid arthritis. Its pharmacological characteristics, clinical efficacy, effectiveness and safety are discussed in this article. Based on the summarized studies, adalimumab was shown to be effective in patients with active disease. Its beneficial effect can start as early as 1 week after the first dose, and be maintained in responders for up to 5 years. Adalimumab is generally well tolerated. The most common adverse event is injection site reactions. There is no increased rate of serious adverse events in trials, but serious infections, such as tuberculosis, have been reported in larger observational studies and remain a concern to screen and watch for.

KEYWORDS: adalimumab ■ biologics ■ DMARD ■ monoclonal antibody ■ rheumatoid arthritis ■ safety ■ therapy ■ TNF-α ■ TNF-α inhibitor

Jean H Tayar*[1], Maria A Lopez-Olivo[1] & Maria E Suarez-Almazor[1]

[1]Department of General Internal Medicine, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1465, Houston, TX 77030, USA
**Author for correspondence:*
Tel.: +1 713 563 4452
Fax: +1 713 563 4491
jhtayar@mdanderson.org

Rheumatoid arthritis (RA) is the most common chronic autoimmune inflammatory arthritis, with a prevalence of approximately 1%, with women being affected twice as often as men [1]. The pathogenesis of RA involves an overexpression of many inflammatory cytokines, including TNF-α, certain other interleukins (ILs) and proteinases. This results in the formation and perpetuation of an inflammatory synovitis that may lead to cartilage and bone destruction, and most patients will have evidence of joint erosions in the first year of the disease [2,3]. The progression of RA leads to a variety of characteristic signs and symptoms, including pain and swelling of the synovial joints, constitutional symptoms and extra-articular involvement. RA can ultimately lead to functional decline and disability, with reduced quality of life and premature mortality, causing a great economic impact to society [2]. The objective of RA treatment is to control the clinical symptoms and slow or stop the radiographic progression and structural damage to improve function and quality of life. Traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, remain the basis of RA therapy, and should be initiated early in the course of the disease [4]. In the last few decades, advances in the understanding of the pathogenesis of RA and the inflammatory cascade led to the introduction of biologic response modifiers (BRMs), also known as biologic DMARDs, a class of medication that can further improve clinical outcomes. These agents work by selective blockade of certain molecules of the inflammatory cascade, resulting in a significant reduction of inflammation. They are mostly used in conjunction with methotrexate for patients who fail with, or are unable to tolerate, traditional DMARDs [4,5]. Available BRMs include TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab and certolizumab), which are currently the most commonly used biologic agents. Other BRMs are anakinra (IL-1 receptor antagonist), abatacept (cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin), rituximab (anti-CD20 antibody) and tocilizumab (IL-6 inhibitor). Newer BRM agents are continually being evaluated. This article focuses on adalimumab, a commonly used TNF-α inhibitor that has been on the market for 8 years.

Adalimumab: a TNF-α inhibitor

TNF-α is one of the inflammatory cytokines induced by RA, and is found in a high concentration in the synovial joints [6]. It works by binding to two types of receptors (p55 and p75), and has the ability to induce other inflammatory cytokines, thereby perpetuating the inflammation cascade and resulting in joint damage. Blocking TNF-α significantly reduces such inflammation and suppresses the formation of invasive pannus. TNF-α inhibitors were introduced as a therapeutic option for RA in 1998, and currently remain the most commonly used BRM. There are five TNF-α inhibitors now licensed (Table 1) with some differences in their structure, function and administration routes. Studies have

Future Medicine part of fsg

Table 1. TNF-α inhibitors approved for rheumatoid arthritis treatment.

Generic name	Brand name	Molecule	Dosing
Adalimumab	Humira®	Human monoclonal antibody	sc. injection, 40 mg every 2 weeks
Etanercept	Enbrel®	p75 receptor-Fc fusion protein	sc. injection, 50 mg every week
Infliximab	Remicaid®	Chimeric monoclonal antibody	iv. infusion, 3 mg/kg at 0, 2 and 6 weeks followed by maintenance every 4–8 weeks
Golimumab	Simponi®	Human monoclonal antibody	sc. injection, 50 mg every month
Certolizumab	Cimzia®	Human, pegylated monoclonal antibody	sc. injection, 200–400 mg every 2–4 weeks

iv.: Intravenous; sc.: Subcutaneous.

shown that they are all highly effective in reducing joint damage and disability, and improving quality of life, especially when combined with methotrexate [4,6–9]. While TNF-α inhibitors, like the other BRMs, are mostly used when patients with active RA do not have a satisfactory response to traditional DMARDs [4,10,11,201], they can also be chosen as first-line therapy in severe cases or when traditional DMARDs are contraindicated [10,12]. Adalimumab was the third TNF-α inhibitor to be introduced, and the first fully human monoclonal antibody of the group. It is currently widely used across the world for the treatment of RA. Adalimumab is also approved by the US FDA and the EMA for the treatment of ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis and Crohn's disease.

To retrieve the evidence for this review, the authors searched MEDLINE (through PubMed) to identify relevant citations published in English or Spanish. Medical terms related to 'adalimumab' were combined using 'AND' with those related to 'rheumatoid arthritis'. Of 1218 potentially relevant citations, 14 publications reporting on controlled trials, 12 open-label extensions, 38 registry studies and 40 systematic reviews were summarized.

Chemistry

Adalimumab is composed of human-derived heavy and light chain variable regions and human IgG1k constant regions [13]. Each of the two κ light chains consists of 214 amino acid residues with a molecular weight of approximately 49 kDa, and each of the two heavy chains has 451 amino acid residues of approximately 24 kDa. Adalimumab (Humira®) is manufactured by Abbott Bioresearch Center (Worcester, MA, USA). It is genetically engineered and supplied in a preservative-free solution for subcutaneous administration. For production, a Chinese hamster ovary host cell is transfected with a plasmid vector containing the expression cassettes of adalimumab. The resulting adalimumab is then purified through several chromatography steps and is subjected to low pH treatment and nanofiltration. Adalimumab is formulated as a vial, or a single-use prefilled syringe, containing 40 mg of active substance in 0.8 ml of a buffered solution comprised of mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride and polysorbate 80 [14]. Based on EMA documents, adalimumab has a shelf life of 18 months at 2–8°C.

Pharmacodynamics

Adalimumab is a fully human recombinant monoclonal IgG1 antibody against TNF-α (Table 2). It blocks the interaction of TNF-α with its cell surface receptors (p55 and p75; IC_{50}: 10^{-9}–10^{-10} M) by binding to both soluble and receptor-bound TNF-α; it does not bind lymphotoxin (TNF-β). The binding to soluble TNF is highly specific ($K_d = 6 \times 10^{-10}$ M) [13]. Pharmacologic mechanisms of action are triggered at subcellular, cellular and higher levels. Adalimumab effects on RA patients include a rapid reduction of acute-phase reactants with a decrease of serum levels of inflammatory cytokines, IL-6, certain metalloproteinases (MMP-1 and MMP-3) and adhesion molecules responsible for leukocyte migration (i.e., VCAM-1, ICAM-1 and others) [15,16,202].

Pharmacokinetics

In pharmacokinetic studies in healthy adults, the maximum serum concentration of adalimumab

Table 2. Pharmacokinetics studies of adalimumab.

Study	Population	n	ADM doses	T_{max}	C_{max}	t½	$AUC_{0-\infty}$	Bioavailability	Clearance	Distribution volume (l)	Ref.
RCT 1 (DE024)	Healthy male Caucasians	80	1 mg/kg iv. SD 0.1 mg/kg sc. SD 0.3 mg/kg sc. SD 1.0 mg/kg sc. SD	48–336 h	Increased proportionally only at doses of 0.3 and 1 mg/kg (mean: 0.46 ± 0.15 µg/ml)	284–433 h	Mean: 292 ± 95 µg per h/ml	52% (1 mg/kg sc. vs 1 mg/kg iv.)	11–22 ml/h (mean of 0.3 and 1.0 mg/kg sc.)		[202]
OLT 3 (DE029)	Healthy male and female subjects	120	25 mg/ml sc. SD 50 mg/ml sc. SD	130–137 h	4.7–5.0 µg/ml		1221.7–1311.3 mg per h/ml				[202]
OLT 4 (DE015)	Healthy male and female subjects	31	25 mg/ml sc. 50 mg/ml sc. + surfactant 50 mg/ml sc. 50 mg/ml iv. + surfactant	0.7–130 h	4.7–15.07 µg/ml	382–484 h	1256–1884 mg per h/ml		0.0015–0.0021 l/h and 0.19–0.23 ml/min (CL/F)	6.6–7.5	[202]
OLT 5 (DE004)	Patients with RA	24	0.5 mg/kg sc. weekly for 2.5 years			22.4 days			19.08 ml/h	6.8	[202]
RCT 2 (DE001), den Broeder *et al.* (2002)	Patients with RA	120	0.5 mg/kg iv. SD 1.0 mg/kg iv. SD 3.0 mg/kg iv. SD		24.6 (0.5 mg/kg) to 283.7 (10 mg/kg) µg/ml	242–326 h	2729 µg per h/ml (0.5 mg/kg) to 67,115 µg per h/ml (10 mg/kg)		0.012–0.017 l/h†	4.7–5.5	[22]
15 (DE003) continuation 3-year data			5.0 mg/kg iv. SD 10 mg/kg iv. SD						13.47–14.65 ml/h (uninterrupted treatment) 18.72–37.50 ml/h (interrupted)		[202]
RCT 6 (DE005) Weisman *et al.* (2003)	Patients with RA	60	0.25 mg/kg + MTX iv. SD 0.5 mg/kg + MTX iv. SD 1 mg/kg + MTX iv. SD		7.38–116.79 mg/ml	353–464 h	1884–37,964 mg per h/l		0.009–0.012 l/h‡	5.44–5.75	[32]

†*Slightly decreased with increasing dose.*
‡*Linear increase in serum clearance with an increase in total body weight.*
§*Patients who completed the blinded period continued to receive ADM at a dose of 40 mg per week for another year followed by a 6-month follow-up (open-label continuation period).*
¶*No attempt was made to evaluate the impact of MTX in the pharmacokinetics of ADM.*
#*Data provided for the iv. administration only.*
ADM: Adalimumab; $AUC_{0-\infty}$: Area under the plasma concentration–time curve from time zero to infinity; CL/F: Apparent total clearance of the drug from plasma after administration; e2w: Every 2 weeks; MTX: Methotrexate; iv.: Intravenous; OLT: Open-label trial; RA: Rheumatoid arthritis; RCT: Randomized clinical trial; sc.: Subcutaneous; SD: Single dose; t½: Elimination half-life; T_{max}: Time to reach maximum (peak) plasma concentration following drug administration.

Table 2. Pharmacokinetics studies of adalimumab (cont.).

Study	Population	n	ADM doses	T_{max}	C_{max}	t½	$AUC_{0-\infty}$	Bioavailability	Clearance	Distribution volume (l)	Ref.
7 (DE005X) continuation 5-month data			3 mg/kg + MTX iv. SD 5 mg/kg + MTX iv. SD	0.8–2.1 h	18.6–268.5 µg/ml		2407–50,067 µg per h/ml		6.76–10.01 ml/h		[202]
RCT 8 (DE007) van de Putte *et al.* (2003)	Patients with RA	284	20 mg[§] sc./week for 12 weeks 40 mg[§] sc./week for 12 weeks 80 mg[§] sc./week for 12 weeks		5.38–25.24 ng/ml						[29]
RCT 9 (DE009) Weinblatt *et al.* (2003) – ARMADA[¶]	Patients with RA	271	20 mg sc. e2w + MTX 40 mg sc. e2w + MTX 80 mg sc. e2w + MTX		Serum predose concentration increased from 0 at baseline to 3.63 ± 2.36 (20 mg), 7.92 ± 3.87 (40 mg), 13.15 ± 6.92 (80 mg) at 24 weeks						[31]
10 (DE009X) continuation 6–8 months data		250	Data provided only for the 40-mg dose	83.2 ± 62.8 h	9.97 ± 5.58 µg/ml		2563.2 ± 1367.4 µg per h/ml		19.60 ± 9.11 ml/h (CL/F)		[202]
RCT 11 DE010[#] Rau *et al.* (2004)	Patients with RA	54	1 mg/kg iv. for three injections 1 mg/kg sc. for three injections	1.15 ± 1.14 h	30.84 ± 6.56 µg/ml	16.3 ± 6.4 days	5408.72 ± 1750.75 µg per h/l		11.0 ± 4.2 ml/h	5.28 ± 1.1	[27]
RCT 12 (DE011) van de Puttec *et al.* (2004)	Patients with RA	364	20 mg sc. e2w 40 mg sc. e2w 20 mg sc./week 40 mg sc./week		ADM at 20 and 40 mg and every week or every 2 weeks had linear serum concentration time profiles						[30]

[†]*Slightly decreased with increasing dose.*
[‡]*Linear increase in serum clearance with an increase in total body weight.*
[§]*Patients who completed the blinded period continued to receive ADM at a dose of 40 mg per week for another year followed by a 6-month follow-up (open-label continuation period).*
[¶]*No attempt was made to evaluate the impact of MTX in the pharmacokinetics of ADM.*
[#]*Data provided for the iv. administration only.*
ADM: Adalimumab; $AUC_{0-\infty}$: Area under the plasma concentration–time curve from time zero to infinity; CL/F: Apparent total clearance of the drug from plasma after administration; e2w: Every 2 weeks; MTX: Methotrexate; iv.: Intravenous; OLT: Open-label trial; RA: Rheumatoid arthritis; RCT: Randomized clinical trial; sc.: Subcutaneous; SD: Single dose; t½: Elimination half-life; T_{max}: Time to reach maximum (peak) plasma concentration following drug administration.

Table 2. Pharmacokinetics studies of adalimumab (cont.).

Study	Population	n	ADM doses	T_{max}	C_{max}	t½	$AUC_{0-\infty}$	Bioavailability	Clearance	Distribution volume (l)	Ref.
RCT 14	Healthy Japanese males	20	0.1 mg/kg sc. SD	168	0.47 ± 0.14 µg/ml	14.6 ± 3.2 days	349 ± 106 µg per h/ml				[202]
RCT 16	Japanese patients with RA	352	80 mg sc. e2w 40 mg sc. e2w 20 mg sc. e2w		ADM at 20, 40 and 80 mg had linear serum concentration–time profiles						[202]

†Slightly decreased with increasing dose.
‡Linear increase in serum clearance with an increase in total body weight.
§Patients who completed the blinded period continued to receive ADM at a dose of 40 mg per week for another year followed by a 6-month follow-up (open-label continuation period).
¶No attempt was made to evaluate the impact of MTX in the pharmacokinetics of ADM.
#Data provided for the iv. administration only.
ADM: Adalimumab; $AUC_{0-\infty}$: Area under the plasma concentration–time curve from time zero to infinity; CLIF: Apparent total clearance of the drug from plasma after administration; e2w: Every 2 weeks; MTX: Methotrexate; iv.: Intravenous; OLT: Open-label trial; RA: Rheumatoid arthritis; RCT: Randomized clinical trial; sc.: Subcutaneous; SD: Single dose; t½: Elimination half-life; T_{max}: Time to reach maximum (peak) plasma concentration following drug administration.

was 4.7 ± 1.6 µg/ml, reached in 131 ± 56 h after a single 40-mg subcutaneous dose, with an estimated 64% bioavailability. In RA patients, the mean half-life was approximately 2 weeks (range: 10–20 days) and the trough concentrations for the usual dose of 40 mg every other week was 5 µg/ml, which increased to 8–9 µg/ml for those also treated with methotrexate [203]. Clearance of adalimumab tends to decrease with age, and there are no gender differences in its pharmacokinetics. There are no available pharmacokinetic data for patients with renal or hepatic impairment. The recommended dosing schedule for adalimumab is a subcutaneous injection of 40 mg every other week, which can be increased to weekly injections. Absorption and distribution of adalimumab are slow, with peak serum concentrations reached 4–7 days after administration. Adalimumab volume of distribution ranges from 4.7 to 6 L. In the synovial fluid of RA patients, adalimumab concentrations have ranged from 31 to 96% of those found in the serum. When combined with methotrexate, adalimumab increases the clearance of methotrexate by 40% (4.39 vs 6.16 l/h) [16,17].

Clinical efficacy

The ACR20, 50 and 70 response criteria [18] are commonly used efficacy end points in clinical trials evaluating RA therapies. They include number of tender and swollen joints; patient assessments of pain, disease activity and disability (Disability Index of the Health Assessment Questionnaire [HAQ]); doctor global assessment of disease activity; and inflammatory biomarkers (erythrocyte sedimentation rate and/or C-reactive protein). Other common outcome measures used are the European League Against Rheumatism response based on the disease activity score (DAS), radiographic progression and other disability assessments. In this section, we review data from published randomized controlled trials (RCTs), including Phase I trials [19–32].

Of the 14 published trials, three studies were Phase I, four were Phase II and seven were Phase III (Table 3). All studies included patients aged 18 years or older, with a diagnosis of RA based on the 1987 revised criteria established by the ACR; 11 studies included patients with long-standing active disease who had failed treatment with at least one DMARD (most commonly methotrexate). In three studies participants had early RA with no prior methotrexate therapy (methotrexate-naive patients) [19,20,28]. When allowed, DMARDs were provided at stable doses (e.g., methotrexate 7.5–25 mg per

week). Participants were excluded if they had significant comorbidities, were pregnant or had previously received other BRMs. All except one were multicenter studies: four were conducted in the USA and Canada, three in Canada, one each in Taiwan, Korea, UK, Japan and France, and two included patients from Europe, Australia and North America. All but one study were fully sponsored by Abbott; the remaining study [28] was supported by a grant from the French Society of Rheumatology, but adalimumab was provided by Abbott. A total of 4126 participants were included in the trials; 1275 were assigned to adalimumab monotherapy, 1503 to adalimumab combined with methotrexate or any traditional DMARD, and 1348 to a control group (placebo, methotrexate or any other traditional DMARD). Of the 2778 patients assigned to the intervention groups, 152 received adalimumab intravenously and 2626 subcutaneously. Participants of the Phase I studies were followed for 4 weeks during the blinded period, and then for 1 or 2 years in open-label studies evaluating doses ranging from 0.25 to 10 mg/kg intravenously, or 1 mg/kg subcutaneously. Two Phase II studies had a follow-up of 12 weeks, and the remaining studies had at least 24 weeks of double-blind treatment phase. Doses included in the Phase II and III studies were 20, 40 and 80 mg subcutaneously weekly or every other week.

In most trials, the ACR20 response rate (RR) was the primary end point, except for the Keystone *et al.* [24], Furst *et al.* [23] and Bejarano *et al.* [19] trials, where primary end points were radiographic progression, safety and job loss, respectively.

For this article, we have chosen to summarize the results of four outcomes: ACR50; mean change from baseline to final follow-up visit of the DAS; radiographic progression measured by the total Sharp score; and the disability index measured by the HAQ (Table 4).

The ACR50 RRs for the adalimumab groups were significantly higher than in the control groups in most trials, except in two trials of methotrexate-naive patients: Bejarano *et al.* [19], where there were no differences at 56 weeks, and the GUEPARD trial [28], where ACR50 responses improved at 12 weeks, but were similar between groups at 52 weeks. Furthermore, Breedveld *et al.* [20] found a higher ACR50 RR only when comparing the adalimumab plus methotrexate combination group with adalimumab or methotrexate monotherapy. In most studies, the individual components of the ACR response criteria (tender and swollen joint counts, physician and patient global assessments, HAQ scores and acute phase reactants) were also improved in the adalimumab groups compared with controls. Of note, RRs with adalimumab were evident within 2 weeks of treatment in many of the trials.

Compared with placebo, patients who failed other DMARDs had a significant reduction in the DAS at the final visit, from baseline, in Phase II and III studies [29,30]. These results were consistent across all tested dosages of adalimumab (20 and 40 mg weekly or every other week, and 80 mg weekly) and occurred early (at 2 weeks) in the course of the trials. For methotrexate-naive patients, the PREMIER [20] and GUEPARD [28] trials had a significantly higher proportion of patients treated with adalimumab combined with methotrexate achieving a DAS of less than 2.6 units versus methotrexate or adalimumab monotherapy at 52 and 104 weeks, and similar results were observed at 56 weeks by Bejarano *et al.* [19]. On the other hand, the third trial assessing methotrexate-naive patients (the GUEPARD trial) only found a significant improvement in the DAS at 12 weeks and not at the final visit (52 weeks) between combination therapy (adalimumab and methotrexate) and methotrexate groups. When comparing weekly with every other week subcutaneous adalimumab, similar reductions in the DAS were found [30].

Only three trials had radiographic assessment in their outcomes. Two of them, the PREMIER study (a methotrexate-naive trial) and the Keystone *et al.*, trial showed significant improvement in total Sharp x-ray scores for adalimumab with methotrexate compared with methotrexate alone or with adalimumab monotherapy [20,24]. However, the GUEPARD trial (methotrexate naive-patients) found no differences between their two groups (methotrexate or methotrexate with adalimumab) at 52 weeks [28].

Functional outcomes using the HAQ are also summarized in Table 4. When assessed, a greater absolute improvement of the HAQ score from baseline to final visit was observed in patients taking adalimumab compared with controls in most trials except for the GUEPARD trial, where no significant statistical difference was found among its two groups of methotrexate-naive patients [28]. In the PREMIER trial, at 1 year patients in the combination therapy group (methotrexate with adalimumab) had a significant improvement in the HAQ score compared with either drug as monotherapy, but at the final 2-year visit this improvement in the combination group remained significant only when compared with methotrexate monotherapy [20].

Table 3. Study and participant characteristics of the included clinical trials.

Study (year)	Duration	Setting		Eligibility criteria					Age (years)	DD (years)	Funding	Primary outcomes	Ref.
		Sites	*Location*	*Age (years)*	*1987 ACR criteria*	*Active disease*	*MTX naive*	*Failed other biologics*					
Phase I studies													
den Broeder *et al.* (2002)	29 days	3	Europe	18	ns	Yes	No	No	Median: 55	11.5	Abbott GmbH & Co. KG	Pharmacokinetics	[22]
Weisman *et al.* (2003)	4 weeks	6	USA and Canada	18	Yes	Yes	No	No	Mean: 52.9	15.7	Abbott Laboratories	Efficacy and pharmacokinetics	[32]
Rau *et al.* (2004)	29 days	4	Europe	18	Yes	Yes	No	No	Mean: 53.2	11.1	Abbott Laboratories	Efficacy and safety	[27]
Phase II studies													
Van De Putte *et al.* (2003)	12 weeks	25	Europe	18	Yes	Yes	No	No	Mean: 52.4	10	Abbott Laboratories		[29]
Weinblatt *et al.* (2003; ARMADA)	24 weeks	35	USA and Canada	18	Yes	Yes	No	ns	Mean: 55.5	12.3	Abbott Laboratories and Knoll Pharmaceuticals	Efficacy and safety	[31]
Furst (2003) (STAR)	24 weeks	69	USA and Canada	18	Yes	Yes	No	No	Mean: 55.4	10.4	Abbott Laboratories	Safety	[23]
Chen *et al.* (2009)	12 weeks	1	Taiwan	29	Yes	Yes	No	No	Median: 53	6.7	ns		[21]
Phase III studies													
Keystone *et al.* (2004; DE019)	52 weeks	89	USA and Canada	18	Yes	Yes	No	No	Mean: 56.5	10.9	Abbott Laboratories	Radiographic	[24]
Van De Putte *et al.* (2004)	26 weeks	52	Europe, Canada and Australia	18	Yes	Yes	No	ns	Median: 53	11	Abbott GmbH & Co. KG, Abbott Laboratories	Efficacy and safety	[30]
Kim *et al.* (2007)	24 weeks	6	Korea	18	Yes	Yes	No	ns	Mean: 49.1	6.8	Abbott Laboratories	Efficacy and safety	[25]
Miyasaka (2008; (CHANGE)	24 weeks	68	Japan	20	Yes	Yes	No	No	Mean: 54.9	9.5	Abbott Japan and Eisai Co.	Efficacy and safety	[26]
Bejarano *et al.* (2008)	56 weeks	10	UK	18	Yes	No	Yes	No	Median: 47	0.72	Abbott Laboratories	Job loss	[19]
Breedveld *et al.* (2006; PREMIER)	104 weeks	133	Australia, Europe and North America	18	Yes	Yes	Yes	No	Median: 52	0.73	Abbott Laboratories	Efficacy and safety	[20]
Soubrier *et al.* (2009; GUEPARD)	52 weeks	13	France	18	Yes	Yes	Yes	No	Mean: 47.7	0.36	French Society of Rheumatology, Abbott France	Efficacy	[28]

DD: Disease duration; MTX: Methotrexate; ns: Not specified.

Table 4. Reported efficacy outcomes of the included clinical trials.

Study (year)	Duration	Groups	n	ACR50 (%)	DAS†	Radiographic progression†‡	HAQ†§	Ref.
Phase I studies								
den Broeder *et al.* (2002)	29 days	ADM 0.5 mg/kg iv. SD	17	18	0.16 (95% CI: -0.32–0.64)	NA	-0.25	[22]
		ADM 1 mg/kg iv. SD	18	17	-0.81 (95% CI: -1.31 to -0.31)		-0.52	
		ADM 3 mg/kg iv. SD	18	28	-1.05 (95% CI: -1.54 to -0.55)		-0.49	
		ADM 5 mg/kg iv. SD	18	28	-1.52 (95% CI: -2.08 to -0.96)		-0.23	
		ADM 10 mg/kg iv. SD	18	17	-1.08 (95% CI: -1.54 to -0.62)		-0.32	
		PBO	31	0	Mean difference range: 0.04–0.38		-0.13	
Weisman *et al.* (2003)	4 weeks	ADM 0.25 mg/kg iv. SD + MTX	9	33		NA	-0.30	[32]
		ADM 0.5 mg/kg iv. SD + MTX	9	44			-0.30	
		ADM 1 mg/kg iv. SD + MTX	9	11			-0.10	
		ADM 3 mg/kg iv. SD + MTX	9	22			-0.20	
		ADM 5 mg/kg iv. SD + MTX	9	11			-0.30	
		PBO + MTX	15	0			-0.20	
Rau *et al.* (2004)	29 days	ADM 1 mg/kg iv. SD + MTX	18	11	-0.82 ± 0.47	NA	-0.27	[27]
		ADM 1 mg/kg sc. SD + MTX	18	17	-0.65 ± 0.78		-0.10	
		PBO + MTX	18	0	-0.17 ± 0.55		+0.06	
Phase II studies								
Van De Putte *et al.* (2003)	12 weeks	ADM 20 mg/week, sc.	71	24	-1.8 ± 1.0	NA	-0.45 ± 0.46	[29]
		ADM 40 mg/week, sc.	70	27	-2.1 ± 1.3		-0.47 ± 0.43	
		ADM 80 mg/week, sc.	72	19	-2.0 ± 1.2		-0.48 ± 0.50	
		PBO	70	1	-0.5 ± 1.1		-0.04 ± 0.37	
Weinblatt *et al.* (2003) (ARMADA)	24 weeks	ADM 20 mg e2w, sc. + MTX	69	32		NA	-0.54 ± 0.58	[31]
		ADM 40 mg e2w, sc. + MTX	67	55			-0.62 ± 0.63	
		ADM 80 mg e2w, sc. + MTX	73	43			-0.59 ± 0.53	
		PBO + MTX	62	8			-0.27 ± 0.57	
Furst *et al.* (2003) (STAR)	24 weeks	ADM 40 mg e2w, sc. + DMARDs	318	29		NA		[23]
		PBO + DMARDs	318	11				
Chen *et al.* (2009)	12 weeks	ADM 40 mg e2w, sc. + MTX	35	34		NA	-0.60	[21]
		PBO + MTX	12	17			-0.10	
Phase III studies								
DMARD failure								
Keystone *et al.* (2004) (DE019)	52 weeks	ADM 20 mg e2w, sc. + MTX	207	38		0.8 ± 4.9	-0.61 ± 0.55	[24]
		ADM 40 mg e2w, sc. + MTX	212	42		0.1 ± 4.8	-0.59 ± 0.57	
		PBO + MTX	200	10		2.7 ± 6.8	-0.25 ± 0.56	

†*Numbers indicate mean difference ± standard deviation.*
‡*Total Sharp score ± standard deviation (lower absolute change indicates less radiographic changes over time).*
§*Greater absolute change indicates less disability.*
ACR50: Percentage of study participants achieving 50% of the ACR response criteria; ADM: Adalimumab; DAS: Disease activity score; DMARD: Disease-modifying antirheumatic drug; e2w: Every 2 weeks (every other week); HAQ: Health Assessment Questionnaire; iv.: Intravenous; MTX: Methotrexate; NA: Not applicable; PBO: Placebo; sc.: Subcutaneous; SD: Single dose.

Table 4. Reported efficacy outcomes of the included clinical trials (cont.).

Study (year)	Duration	Groups	n	ACR50 (%)	DAS†	Radiographic progression†‡	HAQ†§	Ref.
Phase III studies (cont.)								
DMARD failure (cont.)								
Van de Putte *et al.* (2004)	26 weeks	ADM 20 mg e2w, sc. + PBO	106	19	-1.3 ± 1.6	NA	-0.29 ± 0.63	[30]
		ADM 20 mg/w, sc.	112	21	-1.6 ± 1.7	NA	-0.39 ± 0.62	
		ADM 40 mg e2w, sc. + PBO	113	22	-1.7 ± 1.6	NA	-0.38 ± 0.60	
		ADM 40 mg/w, sc.	103	35	-2.0 ± 1.6	NA	-0.49 ± 0.54	
		PBO	110	8	-0.7 ± 1.3	NA	-0.07 ± 0.49	
		ADM 40 mg e2w, sc. + PBO	274	37	25% had DAS of <2.6	5.5	-0.90 ± 0.7	
		PBO + MTX	257	43	25% had DAS of <2.6	10.4	-0.90 ± 0.6	
Kim *et al.* (2007)	24 weeks	ADM 40 mg e2w, sc. + MTX	65	44		NA	-0.50 ± 0.55	[25]
		PBO + MTX	63	15			-0.20 ± 0.50	
Miyasaka (2008) (CHANGE)	24 weeks	ADM 20 mg e2w, sc.	87	16		NA	-0.20 ± 0.50	[26]
		ADM 40 mg e2w, sc.	91	24			-0.20 ± 0.60	
		ADM 80 mg e2w, sc.	87	32			-0.40 ± 0.60	
		PBO	87	6			+0.10 ± 0.6	
MTX naive								
Bejarano *et al.* (2008)	56 weeks	ADM 40 mg e2w, sc. + MTX	75	56		NA	-0.70 ± 0.60	[19]
		PBO + MTX	73	45			-0.40 ± 0.70	
Breedveld *et al.* (2006) (PREMIER)	104 weeks	ADM 40 mg e2w, sc. + MTX	268	59	49% had DAS of <2.6	1.9	-1.0 ± 0.7	[20]
Soubrier *et al.* (2009) (GUEPARD)	52 weeks	ADM 40 mg e2w, sc. + MTX	33	68	36% had DAS of <2.6	1.9 ± 4.0	-1.0 (95% CI: -0.81 to -1.2)	[28]
		MTX	32	67	13% had DAS of <2.6	1.8 ± 4.7	-0.93 (95% CI: -0.69 to -1.2)	

†*Numbers indicate mean difference ± standard deviation.*
‡*Total Sharp score ± standard deviation (lower absolute change indicates less radiographic changes over time).*
§*Greater absolute change indicates less disability.*
ACR50: Percentage of study participants achieving 50% of the ACR response criteria; ADM: Adalimumab; DAS: Disease activity score; DMARD: Disease-modifying antirheumatic drug; e2w: Every 2 weeks (every other week); HAQ: Health Assessment Questionnaire; iv.: Intravenous; MTX: Methotrexate; NA: Not applicable; PBO: Placebo; sc.: Subcutaneous; SD: Single dose.

When compared, there were no major differences in functional outcomes found between adalimumab subcutaneous doses of 20, 40 or 80 mg given every other week [26,29–31].

All of these results support the efficacy of adalimumab at the approved dose of 40 mg subcutaneously every other week in combination with methotrexate in the treatment of RA.

Adalimumab compared with other BRMs

There are few comparative data between different BRMs. One controlled cohort study [33] and one RCT [34] compared adalimumab with other TNF-α inhibitors (etanercept and infliximab). No statistically significant differences in efficacy were found between patients receiving adalimumab or etanercept, with a mean change in the DAS of -3.3 with adalimumab and -2.8 with etanercept at 12 months [33]. The second study compared mean changes in the DAS from 4 to 12 weeks in patients receiving different TNF-α inhibitors (adalimumab, etanercept or infliximab) in combination with methotrexate or leflunomide [34]. The observed absolute changes were not statistically different between the six groups.

Clinical effectiveness

In this section, we summarize the evidence on clinical effectiveness on the basis of the

continuation of adalimumab therapy beyond RCTs, or in registry studies.

During the open-label extension of the clinical trials, the effectiveness of adalimumab in achieving an ACR50 was better when combined with methotrexate [35–46]. At 2 and 5 years, inhibition of structural damage was also maintained for responders, showing less or no radiographic progression in 54 and 50% of the patients, respectively. Similarly, more than 80% of the patients maintained an improvement in the disability score (HAQ <0.5) through 5 years of follow-up [37]. Regarding patients with prior treatment using other TNF-α inhibitors, the ReAct open-label trial found that adalimumab 40 mg every other week had a significant clinical benefit at 12 weeks among the 899 patients previously treated with etanercept or infliximab (33% ACR50 response; 23% good European League Against Rheumatism response; 12% achieved a DAS <2.6; and 13% achieved a HAQ disability index score <0.5) [47]. Another comparative controlled study also found adalimumab to be effective for RA patients after 12 months when switching from infliximab with similar ACR20 and DAS28 RRs compared with patients on adalimumab as first TNF-α inhibitor therapy [48]. These results, along with other similar findings from certain registries (Stockholm TNF-α inhibitors follow-up registry [49] and the Finnish Register of Biological Treatment [50]), suggest that adalimumab is also effective when given to patients with prior TNF-α inhibitors treatment.

Several studies on data from national registries found that the effectiveness of adalimumab was better when combined with methotrexate (or other DMARDs such as leflunomide), and no significant differences were found when comparing the first three approved TNF-α inhibitors (infliximab, etanercept and adalimumab) [42,51,52]. The Danish Registry for Biologic Therapies in Rheumatology (DANBIO) registry on the other hand reported better odds ratios (ORs) for achieving an ACR70 response at 6 months for adalimumab compared with infliximab (OR: 2.1; 95% CI: 1.5–2.8), and similar results when compared with etanercept (OR: 1.2; 95% CI: 0.82–1.6) [53]. The DANBIO findings were echoed by data from the Dutch RA Monitoring registry where at 12 months, the mean scores on the DAS28 and Short Form 36 items physical component scale showed greater benefit for adalimumab and etanercept compared with infliximab ($p < 0.001$). In addition, adalimumab showed a significant reduction in the DAS28 at 12 months compared with etanercept ($p = 0.031$) [54]. One study reporting radiographic changes (DANBIO registry) found that patients with RA had a significant reduction in radiographic progression while on TNF-α inhibitors (adalimumab, etanercept or infliximab) compared with the prior traditional DMARD treatment period (median radiographic progression rate decreased from 0.7 to 0 total Sharp score units/year when started TNF-α inhibitors $p < 0.0001$) [55].

Finally, indirect comparisons among different BRMs in several meta-analysis show that adalimumab and other biologics, when combined with methotrexate, are more efficacious than placebo or controls. Some reviews did not find significant differences among biologics [56–58], while others reported potential benefit of one biologic over the others. A large network meta-analysis including six Cochrane reviews reported a significantly greater ACR50 response comparing adalimumab with anakinra [59]. In one review, tocilizumab had better ACR70 RRs compared with TNF-α inhibitors (relative risk: 1.8; 95% CI: 1.2–2.6) [60] and etanercept had lower ACR20, 50 and 70 responses compared with adalimumab (relative risk: 0.46, 95% CI: 0.34–0.61; 0.37, 95% CI: 0.22–0.60; 0.44, 95% CI: 0.21–0.93, respectively) [61]. One meta-analysis of 29 RCTs showed that adalimumab and etanercept monotherapy when given to methotrexate-naive patients with short disease duration (<3 years) were more effective than methotrexate alone in slowing radiographic joint damage [62].

The available data appear to support that adalimumab is most effective when given in combination with methotrexate [35–46,63]. It has been recommended that infliximab should be administered in conjunction with methotrexate [62] because it is a chimeric monoclonal antibody that can elicit humoral immune responses (neutralizing antibodies) in the recipient [64]. Adalimumab is a fully human-derived antibody, so it is less likely to elicit an immune response [65,66]. However, studies have shown that up to 44% of patients treated with adalimumab have circulating antibodies against this agent [25,67], and that the presence of such autoantibodies was associated with low functional drug levels and decreased clinical response [68]. Therefore, the addition of methotrexate, as is the case for infliximab, could result in better efficacy [67,69]. Furthermore, combination therapies in RA are usually more effective than monotherapy, thus adding methotrexate to a biologic agent could also enhance its efficacy by targeting additional pathogenic pathways.

Withdrawals, safety & tolerability

Adalimumab is generally well tolerated. Data on withdrawals and adverse events (AEs) are displayed in TABLE 5.

Withdrawals

There were no significant differences in the rate of withdrawals between intervention and control groups in the trials at 4 or 12 weeks of follow-up. However, at 24–26 weeks, results were mixed; two studies reported significantly less withdrawals in the adalimumab group than in controls [25,30], whereas two other studies reported similar rates between groups [23,26]. At 52–56 weeks, total withdrawal rates were lower in the adalimumab combined with methotrexate group compared with methotrexate monotherapy [19,24]. In the PREMIER trial, at 104 weeks, patients in the methotrexate or adalimumab monotherapy groups had significantly higher withdrawal rates compared with the adalimumab plus methotrexate combination therapy group, mostly due to lack of efficacy [20].

Data from registries on discontinuation rates compared different drugs or combinations. After 36 months, the discontinuation rates observed in the Rheumatoid Arthritis Observation of Biologic Therapy registry were 46.3, 51.3 and 61.5% for combinations of etanercept, adalimumab and infliximab with methotrexate, respectively, and somewhat higher rates for the same BRMs when combined with leflunomide (53.4, 63.1 and 67.1%, respectively) [42]. In the DANBIO registry, the hazard ratios (HRs) for drug withdrawal at 48 months were significantly higher for infliximab infusions compared with the subcutaneously administered BRMs, etanercept and adalimumab (HR: 2.0; 95% CI: 1.6–2.4 and HR: 1.4; 95% CI: 1.2–1.6, respectively), and also higher when comparing adalimumab with etanercept (HR: 1.5; 95% CI: 1.2–1.8) [53]. On the other hand, the RADIUS 1 study, a 5-year observational registry of patients with RA, found similar discontinuation rates due to lack of efficacy among TNF-α inhibitors (etanercept 19%, infliximab 19% and adalimumab 20%), and somewhat lower rates due to AEs for etanercept (etanercept 14%, infliximab 22% and adalimumab 17%) [70]. In the Lombardy Rheumatoid Arthritis Network registry, the probability of continuing TNF-α inhibitors ranged from 78.8% after 12 months to 52.9% after 36 months, with similar dropout rates for lack of efficacy and AEs. After 36 months, the probability of continuing on etanercept (62.5%) was significantly greater compared with infliximab (49.1%) or adalimumab (53.6%) [71]. An Italian registry, the Gruppo Italiano Studio Early Arthritis reported that after 4 years, the global retention rate of TNF-α inhibitors was 42% [72]. In a more recent study, this rate was found to considerably decrease after the fifth year of therapy [73].

Total AEs

The most common AEs were injection site reactions, abdominal pain, headache and hypertension. Total AE rates, as well as serious AE rates, were mostly similar between groups at all follow-up periods (TABLE 5). Although, injection site reactions occurred more often in the adalimumab group, with a rate of up to 20% compared with the control group rate of 14%; these reactions were mostly mild-to-moderate, rarely leading to discontinuation of therapy. Only four out of 2334 patients treated with adalimumab had systemic reactions considered to be anaphylactic.

Infections

Data from Phase III trials showed that the rate of total infections was similar across groups. In the longest follow-up trial of 104 weeks, the incidence of infections was; 123 events per 100 patient-years in the combined adalimumab plus methotrexate group, 110 events per 100 patient-years in the adalimumab monotherapy group, and 119 events per 100 patient-years in the methotrexate monotherapy group [20]. Most were upper respiratory tract infections, bronchitis and urinary tract infections. In an analysis of 71 studies including 23,458 patients, the most frequently reported serious AEs across indications were infections [74].

Serious infections including sepsis, tuberculosis and other opportunistic infections were reported in clinical trials with adalimumab with rates ranging from 0 to 9% in the adalimumab groups and from 0 to 3% in the control groups. In surveillance studies reported by Abbott, in 22,026 patients treated with adalimumab, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive tuberculin test conversion was 0.07 per 100 patient-years. Other serious opportunistic infections, some fatal, have been reported in the trials at an overall rate of 0.07 per 100 patient-years. Long-term surveillance reports on adalimumab did not show an increased frequency in infections (or serious AEs) after exposure to the drug during additional years in patients with RA [75–77].

Data from registries showed an overall incidence rate for serious infection to be between 31

Table 5. Reported safety outcomes of the included clinical trials.

Study	Groups	n	Withdrawals			Total AEs	Infections	Serious AEs	Serious Infections	Ref.
			Total	Lack of efficacy	AEs					
Week 4										
den Broeder *et al.* (2002)	ADM 0.5 mg/kg iv. SD	17	1 (6%)	NA	1 (6%)	15 (88%)	NA	1 (6%)	NA	[22]
	ADM 1 mg/kg iv. SD	18	0	NA	0	15 (83%)	NA	1 (6%)	NA	
	ADM 3 mg/kg iv. SD	18	0	NA	0	18 (100%)	NA	0	NA	
	ADM 5 mg/kg iv. SD	18	0	NA	0	11 (61%)	NA	0	NA	
	ADM 10 mg/kg iv. SD	18	0	NA	0	16 (89%)	NA	0	NA	
	PBO	31	0	NA	0	27 (87%)	NA	0	NA	
Weisman *et al.* (2003)	ADM 0.25 mg/kg iv. SD+MTX	9	NA	NA	All ADM groups: 3 (7%)	All ADM groups: 30 (67%)	NA	NA	All ADM groups: 1 (2%)	[32]
	ADM 0.5 mg/kg iv. SD + MTX	9	NA	NA			NA	NA		
	ADM 1 mg/kg iv. SD + MTX	9	NA	NA			NA	NA		
	ADM 3 mg/kg iv. SD + MTX	9	NA	NA			NA	NA		
	ADM 5 mg/kg iv. SD + MTX	9	NA	NA			NA	NA		
	PBO + MTX	15	1 (7%)	1 (7%)	0	9 (60%)	NA	NA	0	
Rau *et al.* (2004)	ADM 1 mg/kg iv. SD + MTX	18	1 (6%)	1 (6%)	0	6.2 pt-yr	NA	1 (6%)	0	[27]
	ADM 1 mg/kg sc. SD + MTX	18	0	0	0	6.1 pt-yr	NA	1 (6%)	0	
	PBO + MTX	18	0	0	0	8.6 pt-yr	NA	1 (6%)	0	
Week 12										
Van de Putte *et al.* (2003)[†]	ADM 20 mg/week sc.	71	4 (6%)	2 (3%)	0	NA	NA	2 (3%)	0	[29]
	ADM 40 mg/week sc.	70	4 (6%)	0	3 (4%)	NA	NA	5 (7%)	2 (3%)	
	ADM 80 mg/week sc.	72	3 (4%)	0	2 (3%)	NA	NA	9 (13%)	2 (3%)	
	PBO	70	2 (3%)	1 (1%)	1 (1%)	NA	NA	7 (10%)	0	
Chen *et al.* (2009)	ADM 40 mg sc. e2w + MTX	35	NA	NA	3 (9%)	28 (80%)	NA	5 (14%)	3 (9%)	[20]
	PBO + MTX	12	NA	NA	0	11 (92%)	NA	1 (8%)	0	
Weeks 24–26										
Weinblatt *et al.* (2003) (ARMADA)	ADM 20 mg sc. e2w + MTX	69	All ADM groups: 110 (41%)	All ADM groups: 3 (1%)	4 (6%)	All ADM groups: 2.2 pt-yr	All ADM groups: 1.6 pt-yr	NA	All ADM groups: 2 (0.73%)	[31]
	ADM 40 mg sc. e2w + MTX	67			0			NA		
	ADM 80 mg sc. e2w + MTX	73			1 (1%)			NA		
	PBO + MTX	62	NA	NA	2 (3%)	2.3 pt-yr	1.4 pt-yr	NA	0	

[†]*Values are the number of events per 100 pt-yr.*
ADM: Adalimumab; AE: Adverse event; DMARD: Disease-modifying antirheumatic drug; e2w: Every 2 weeks (every other week); iv.: Intravenous; MTX: Methotrexate; NA: Not available; PBO: Placebo; pt-yr: Patient-year; sc.: Subcutaneous; SD: Single dose.

Table 5. Reported safety outcomes of the included clinical trials (cont.).

Study (year)	Groups	n	Withdrawals			Total AEs	Infections	Serious AEs	Serious Infections	Ref.
			Total	Lack of efficacy	AEs					
Weeks 24–26 (cont.)										
Furst *et al.* (2003) (STAR)	ADM 40 mg sc. e2w + DMARDs	318	28 (9%)	5 (2%)	9 (3%)	275 (87%)	166 (52%)	17 (5%)	4 (1%)	[23]
	PBO + DMARDs	318	30 (9%)	14 (4%)	8 (3%)	263 (83%)	157 (49%)	22 (7%)	6 (2%)	
van de Putte *et al.* (2004)	ADM 20 mg sc. e2w + PBO	106	38 (36%)	31 (29%)	4 (4%)	All ADM groups: 429 (99%)	NA	11 (10%)	All ADM groups: 10 (2%)	[30]
	ADM 20 mg/week sc.	112	33 (29%)	27 (24%)	3 (3%)		NA	18 (16%)		
	ADM 40 mg sc. e2w + PBO	113	32 (28%)	20 (18%)	6 (5%)		NA	13 (12%)		
	ADM 40 mg/week sc.	103	15 (15%)	10 (10%)	3 (3%)		NA	11 (11%)		
	PBO	110	62 (56%)	56 (51%)	1 (0.91%)	105 (96%)	NA	16 (15%)	0	
Kim *et al.* (2007)	ADM 40 mg sc. e2w + MTX	65	14 (22%)	8 (12%)	4 (6%)	54 (83%)	24 (37%)	7 (11%)	3 (5%)	[25]
	PBO + MTX	63	23 (37%)	19 (30%)	4 (6%)	53 (85%)	22 (35%)	6 (10%)	0	
Miyasaka (2008) (CHANGE)	ADM 20 mg sc. e2w	87	7 (8%)	NA	5 (6%)	80 (92%)	30 (35%)	10 (12%)	4 (5%)	[26]
	ADM 40 mg sc. e2w	91	16 (18%)	NA	12 (13%)	90 (99%)	41 (45%)	17 (19%)	6 (7%)	
	ADM 80 mg sc. e2w	87	4 (5%)	NA	3 (3%)	81 (93%)	37 (43%)	8 (9%)	3 (3%)	
	PBO	87	7 (8%)	NA	4 (5%)	71 (82%)	32 (37%)	8 (9%)	1 (1%)	
Weeks 52–56										
Keystone *et al.* (2004) (DE019)	ADM 20 mg/week sc. + MTX	207	48 (23%)	6 (3%)	16 (8%)	All ADM groups: 391 (93%)	33 (16%)	NA	5 (2%)	[24]
	ADM 40 mg sc. e2w + MTX	212	44 (21%)	6 (3%)	28 (13%)		15 (7%)	NA	11 (5%)	
	PBO + MTX	200	60 (30%)	13 (7%)	23 (12%)	181 (91%)	9 (5%)	NA	1 (0.50%)	
Bejarano *et al.* (2008)	ADM 40 mg sc. e2w + MTX	75	25 (33%)	13 (17%)	5 (7%)	68 (91%)	NA	13 (17%)	3 (4%)	[19]
	PBO + MTX	73	37 (51%)	26 (36%)	5 (7%)	64 (88%)	NA	11 (15%	2 (3%)	
Soubrier *et al.* (2009) (GUEPARD)	ADM 40 mg sc. e2w + MTX	33	5 (15%)	0	2 (6%)	NA	NA	5 (15%)	NA	[28]
	MTX	32	3 (9%)	0	1 (3%)	NA	NA	5 (16%)	NA	
Week 104										
Breedveld *et al.* (2006) (PREMIER)	ADM 40 mg sc. e2w + MTX	268	65 (24%)	13 (5%)	32 (12%)	262 (98%)	123 pt-yr†	2.9 pt-yr†	9 (4%)	[20]
	ADM 40 mg sc. e2w + PBO	274	107 (39%)	52 (19%)	26 (10%)	262 (96%)	110 pt-yr†	0.7 pt-yr†	3 (1%)	
	PBO + MTX	257	88 (34%)	46 (18%)	19 (7%)	245 (95%)	119 p-yr†	1.6 pt-yr†	7 (3%)	

†*Values are the number of events per 100 pt-yr.*
ADM: Adalimumab; AE: Adverse event; DMARD: Disease-modifying antirheumatic drug; e2w: Every 2 weeks (every other week); iv.: Intravenous; MTX: Methotrexate; NA: Not available; PBO: Placebo; pt-yr: Patient-year; sc.: Subcutaneous; SD: Single dose.

and 36 per 1000 patient-years for TNF-α inhibitors, mostly lower respiratory tract (34.2%) and skin and soft tissue infections (20.5%). In the Lombardy Rheumatoid Arthritis Network registry, the type of TNF-α inhibitor did not have an impact on the incidence or site of the infections [45], while the Gruppo Italiano Studio Early Arthritis registry reported a higher rate for infliximab (65.1/1000 patient-years; 95% CI: 48.4–81.8) and adalimumab (23.7/1000 patient-years; 95% CI: 13.1–34.2) compared with etanercept (12.8/1000 patient-years; 95% CI: 6.3–19.4) [78]. Data from a large US health-care organization also found that users of other BRMs, including adalimumab, had lower rates of infections requiring hospitalization compared with infliximab (abatacept: HR: 0.68; 95% CI: 0.48–0.96; adalimumab: HR: 0.52; 95% CI: 0.39–0.71; etanercept: HR: 0.64; 95% CI: 0.49–0.84; and rituximab: HR: 0.81; 95% CI: 0.55–1.2) [79].

Regarding the incidence of tuberculosis, patients on TNF-α inhibitors were found to have higher rates than the general population [80–82]. A Spanish registry (Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases) reported an incidence of tuberculosis infection of 0.26 per 1000 patient-years (95% CI: 0.12–0.57) in patients with RA on TNF-α inhibitors. In several registries, this incidence for tuberculosis was higher among infliximab and adalimumab (two monoclonal antibody-based drugs) compared with etanercept, a fusion protein [83–87].

Other opportunistic infections rates are also reported to be higher among TNF-α inhibitors users, and here again those rates were found to be lower with etanercept [84,85].

In addition, prior reports on data from the Rheumatoid Arthritis Observation of Biologic Therapy register suggests that there could be a trend to increased risk of shingles with the monoclonal TNF-α inhibitors (adalimumab and infliximab), and not with etanercept [88]. However, a recent study on data from the British Society for Rheumatology Register found a significantly increased risk of shingles in those patients on TNF-α inhibitors compared with nonbiologic DMARDs, with the lowest risk being for adalimumab (adjusted HR: 1.5; 95% CI: 1.1–2.0) and highest for infliximab (HR: 2.2; 95% CI: 1.4–3.4) [89].

Malignancies

Several observational studies have reported an increased risk of malignancy in patients treated with TNF-α inhibitors [90–96], but the issue remains controversial. Among 2360 patients treated with adalimumab in clinical trials, only 18 patients developed cancer compared with 11 patients of the 1459 patients in the control groups [19,20,23–26,28,30,31], including both solid and hematologic malignancies. Data available from large Swedish registers (more than 6000 patients) did not indicate an increased risk of developing cancer for patients with RA on TNF-α inhibitors (relative risk: 1.00; 95% CI: 0.86–1.15) [91]. Similarly, the French pharmacovigilance system data did not indicate an increased risk of lymphoma during the early phase of TNF-α treatment [83]. In an analysis of 36 studies including 19,041 patients with immune-mediated inflammatory diseases, including RA treated with adalimumab, the cumulative rates of malignancy for treated patients were as expected in the general population [76]. Furthermore, a recent meta-analysis assessing the risk of malignancies in RA patients treated with BRMs (63 RCTs with 29,423 patients) did not find an increased risk of malignancy with the use of adalimumab (OR: 1.8; 95% CI: 0.61–5.4) or the other studied biologics [97].

Autoantibodies

Up to 12% of patients treated with adalimumab in RCTs developed positive antinuclear antibody titers compared with 7% in the control groups [19,20,23–26,28,30,31]. Only four out of 3046 patients treated with adalimumab developed lupus-like syndrome. Rates of conversion to positive anti-dsDNA ranged from 4 to 12%, with none in the controls. Frequency of positive antibodies to adalimumab ranged from 0.7 to 44% [19,20,23–26,28,30,31]. A recent study has demonstrated that more than half of patients on adalimumab produce antibodies to the drug in the first 28 weeks of treatment [98].

Other AEs

In clinical trials, only 4% of RA patients who received the approved dose of adalimumab (40 mg subcutaneously every other week), had alanine aminotransferase elevations (three-times higher than the normal upper limit) compared with 1.5% in the control group.Two cases of demyelinating disease out of 2778 patients treated with adalimumab were reported compared with no events in the control groups [19–32]. Additionally, four patients in the adalimumab groups experienced pancytopenia or agranulocytosis. There were no reports of congestive heart failure; however, based on previous experience with other TNF-α inhibitors, adalimumab is

contraindicated in moderate-to-severe heart failure (New York Heart Association class III/IV) and, according to the manufacturer and the FDA warning label, it should be used with caution in patients with milder heart failure.

Pregnancy

Adalimumab is considered to be a FDA Category B drug. Studies evaluating prenatal toxicity conducted in monkeys at dosages up to 100 mg/kg have revealed no evidence of harm to the fetus. A few case reports reported no neonatal abnormalities or maternal AEs [99–101]. A large survey sent to US rheumatologists found no increase in birth defects or miscarriage rates in 417 women exposed to TNF-α inhibitors during pregnancy [102]. Two studies from the Organization of Teratology Information Specialists reporting on the outcomes of pregnancies with exposure to adalimumab did not find an increased risk or a specific pattern in birth defects [103,104]. The British Society for Rheumatology Biologics Register, on the other hand, found a nonstatistically significant higher rate of spontaneous abortion among patients exposed to anti-TNF inhibitors at the time of conception compared with a control group (24 vs 10%; p = 0.31) [105].

Regulatory affairs

On 31 December 2002, adalimumab received FDA approval. The listed indication is "for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active RA who have an inadequate response to one or more DMARDs"; on 30 July 2004, the indication was expanded to include "improving physical function" of RA patients; on 3 October 2005, the indication was expanded to recently diagnosed patients with moderately-to-severely active RA who were methotrexate naive, and its use was also approved for patients with psoriatic arthritis and ankylosing spondylitis. On 16 February 2007, the precautions section of the package insert was modified to add language regarding immunizations, and it was approved for use in patients with active Crohn's disease who had an inadequate response to conventional therapy or infliximab. On 18 January 2008, adalimumab 40 mg was approved for the treatment of patients with chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and on 21 February 2008 it was approved for juvenile idiopathic arthritis. On 19 November 2009, the FDA requested the manufacturer to include information pertaining to the risk of malignancies with the use of the product, and on 8 April 2010 it required the manufacturer to include a risk evaluation and mitigation strategy to ensure that the benefits of adalimumab outweigh the risks. The same year, the FDA requested that information on the risk of peripheral demyelination disorders, including Guillain–Barre syndrome, demyelinating polyneuropathy, multifocal motor neuropathy and systemic vasculitis, be provided. The following year more information had to be included with the full prescribing information: risk of hepatosplenic T-cell lymphoma, serious infections with the use of abatacept or anakinra, diverticulitis, appendicitis, pancreatitis, Stevens–Jonhson syndrome and optic neuritis. In Europe, adalimumab was first approved in 2003 for the treatment of RA, and later for ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease and psoriasis. The summary of product characteristics can be accessed on the EMA website [204].

Conclusion

Adalimumab is the first fully human monoclonal autoantibody against TNF-α. Published studies have shown that it is efficacious in the management of patients with RA, especially when combined with methotrexate. It is relatively well tolerated, with a safety profile comparable with other TNF-α inhibitors. The most serious concerns about its safety relate to the development of serious infections, but this appears to be comparable with what is observed with other biologics.

Future perspective

The importance of early and effective treatment in patients with RA has been the focus of most recent guidelines for the management of RA [4]. With a better understanding of its pathogenesis, and the development of new targeted therapies, better outcomes are now more attainable. This significant shift in management strategies was driven by the introduction of BRMs almost two decades ago, with TNF-α inhibitors still being the most widely used agents. Some questions regarding TNF-α inhibitors, including adalimumab, remain unanswered, including long-term safety, how much the recommended dose can be escalated in patients with partial response, and whether (and when) therapy can be discontinued in patients achieving remission. Despite the increase in RRs with the current available agents, and more aggressive early therapeutic strategies, a proportion of RA patients do not respond to treatment and their disease progresses. There is a pressing need to better control the disease,

with the ultimate goal of a cure in the future. This is the focus of new research and drug development. There are several new agents in the pipeline that target the same inflammatory pathways as already-approved agents, such as the newer human anti-CD-20 B-cell blocker (ofatumumab [106,107]), other potential B-cell targets (B-lymphocyte stimulator, Toll-like receptors and different surface receptors and markers) and other chemokines. Smaller molecules with enhanced specificity in their function such as the Janus kinase inhibitors are in the final phases of development with promising results [108,109].

Finally, with the increasing numbers of available agents, their variety in toxicity and cost, and the overwhelming data about their efficacy, the choice of therapy has become ever more complex. A major area for development is the identification of predictive disease/patient characteristics or biological markers [110,111], which may help clinicians understand who might respond to one specific compound rather than another. Such

Executive summary

Mechanism of action

- Adalimumab is a recombinant human IgG1 monoclonal antibody that binds to TNF-α and inhibits its inflammatory effects by blocking the interaction with the p55 and p75 cell surface TNF-α receptors.

Pharmacokinetic properties

- Absorption and distribution is slow, with peak serum concentrations being reached approximately 5 days after administration.
- The average absolute bioavailability is estimated in 64% following a single subcutaneous dose of 40 mg.
- Concentrations are dose proportional.
- After a dose of 40 mg:
  - Clearances range from 11–15 ml/h;
  - Distribution volumes range from 5–6 l;
  - Mean terminal phase half-life is 2 weeks.

Clinical efficacy

- The ACR50 response of patients treated with adalimumab plus methotrexate was significantly better than patients treated with methotrexate alone from 4 to 104 weeks. ACR response rates were maintained in the majority of patients followed up to 5 years.
- Clinical remission (DAS28: <2.6) was more likely achieved by patients treated with adalimumab plus methotrexate compared with patients treated with methotrexate monotherapy or adalimumab monotherapy at 52 weeks.
- Reduction in the rate of progression of structural damage is significantly greater in patients treated with combined adalimumab plus methotrexate than with methotrexate or adalimumab alone at 104 weeks.
- All doses of adalimumab in 12 trials showed statistically significantly greater improvement in the disability index of the Health Assessment Questionnaire from baseline to 52 weeks compared with control groups. Only two trials showed no differences at 52 and 104 weeks between groups.

Safety & tolerability

- Most common side effects are:
  - Injection site reactions;
  - Respiratory tract infections;
  - Headache;
  - Abdominal pain;
  - Nausea and vomiting;
  - Rash;
  - Musculoskeletal pain.
- There is potential risk of:
  - Serious infections such as active tuberculosis, sepsis, and opportunistic infections;
  - Worsening of heart failure (New York Heart Association class III/IV);
  - Malignancies and lymphoproliferative disorders;
  - Development of lupus-like syndrome;
  - Birth defects or spontaneous abortions.

Drug interactions

- The concomitant use with other biologic agents can increase the risk of infection and no increase of clinical benefit (specifically anakinra and abatacept).
- Should not be used in patients who have hypersensitivity to adalimumab or to any of the excipients.

Dosage & administration

- Adalimumab is packaged as a 40 mg solution for injection in prefilled syringe. However, it is also available as a vial or prefilled pen. It is administered subcutaneously every other week.

discoveries would help streamline appropriate therapy with a personalized approach that can optimize successes and minimize failures.

Financial & competing interests disclosure

M Suarez-Almazor has a K24 career award from the National Institute for Arthritis, Musculoskeletal and Skin Disorders (NIAMS: grant # AR053593). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Firestein G. Etiology and pathogenesis of rheumatoid arthritis. In: *Kelley's Textbook of Rheumatology*. Harris EJ, Sledge C, Ruddy S (Eds). WB Saunders, Philadelphia, PA, USA, 996–1042 (2005).

2 Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 358(9285), 903–911 (2001).

3 Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann. Rheum. Dis.* 62(7), 611–616 (2003).

4 Saag KG, Teng GG, Patkar NM *et al.* American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 59(6), 762–784 (2008).

▪ **Clinical practice guidelines on the use of biologic disease modifying antirheumatic drugs (DMARDs).**

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

▪ **Update of the 2008 ACR clinical practice guidelines.**

6 Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N. Engl. J. Med.* 355(7), 704–712 (2006).

7 Emery P, Breedveld FC, Hall S *et al.* 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* 372(9636), 375–382 (2008).

8 van der Heijde DM. Overview of radiologic efficacy of new treatments. *Rheum. Dis. Clin. N. Am.* 30(2), 285–293, vi (2004).

9 van der Kooij SM, Allaart CF, Dijkmans BA, Breedveld FC. Innovative treatment strategies for patients with rheumatoid arthritis. *Curr. Opin. Rheumatol.* 20(3), 287–294 (2008).

10 Combe B. Early rheumatoid arthritis: strategies for prevention and management. *Best Pract. Res. Clin. Rheumatol.* 21(1), 27–42 (2007).

11 Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M. Management of rheumatoid arthritis: summary of NICE guidance. *BMJ* 338, b702 (2009).

12 Combe B, Landewe R, Lukas C *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 66(1), 34–45 (2007).

13 Kupper H, Salfeld J, Tracey D, Kalden JR. Approved therapeutics. Adalimumab (Humira). In: *Handbook of Therapeutic Antibodies*, Dübel S (Ed.). Wiley–VCH, Germany, 697 (2008).

14 Furst D, Keystone EC, Weinblatt ME. TNF blockade by the fully human monoclonal antibody, adalimumab (D2E7), in the ARMADA trial results in decreases in serum matrix metalloproteinase levels along with impressive clinical improvement in refractory RA patients. *Arthritis Rheum.* 44(Suppl.), S215 (2001).

15 van Kuijk AW, Degroot J, Koeman RC *et al.* Soluble biomarkers of cartilage and bone metabolism in early proof of concept trials in psoriatic arthritis: effects of adalimumab versus placebo. *PLoS One* 5(9), pii e12556 (2010).

16 Wendling D, Cedoz JP, Racadot E. Serum levels of MMP-3 and cathepsin K in patients with ankylosing spondylitis: effect of TNFα antagonist therapy. *Joint Bone Spine* 75(5), 559–562 (2008).

17 Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J. Rheumatol. Suppl.* 74, 13–18 (2005).

18 Felson DT, Anderson JJ, Boers M *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 38(6), 727–735 (1995).

19 Bejarano V, Quinn M, Conaghan PG *et al.* 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.* 59(10), 1467–1474 (2008).

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

21 Chen DY, Chou SJ, Hsieh TY *et al.* 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.* 108(4), 310–319 (2009).

22 den Broeder AA, van de Putte L, Rau R *et al.* A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-α antibody adalimumab (D2E7) in patients with rheumatoid arthritis. *J. Rheumatol.* 29(11), 2288–2298 (2002).

23 Furst DE, Schiff MH, Fleischmann RM *et al.* Adalimumab, a fully human anti tumor necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J. Rheumatol.* 30(12), 2563–2571 (2003).

24 Keystone EC, Kavanaugh AF, Sharp JT *et al.* 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.* 50(5), 1400–1411 (2004).

▪▪ **52-week trial that was powered to evaluate the efficacy of adalimumab in patients who had an inadequate response to traditional DMARDs.**

25 Kim HY, Lee SK, Song YW *et al.* A randomized, double-blind, placebo-controlled, Phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR J. Rheumatol.* 10(1), 9–16 (2007).

26 Miyasaka N; CHANGE Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. *Mod. Rheumatol.* 18(3), 252–262 (2008).

27 Rau R, Simianer S, van Riel PL *et al.* Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. *Scand. J. Rheumatol.* 33(3), 145–153 (2004).

28 Soubrier M, Puechal X, Sibilia J *et al.* Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. *Rheumatology (Oxford)* 48(11), 1429–1434 (2009).

29 van de Putte LB, Rau R, Breedveld FC *et al.* Efficacy and safety of the fully human anti-tumour necrosis factor α monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, Phase II study. *Ann. Rheum. Dis.* 62(12), 1168–1177 (2003).

30 van de Putte LBA, Atkins C, Malaise M *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann. Rheum. Dis.* 63(5), 508–516 (2004).

31 Weinblatt ME, Keystone EC, Furst DE *et al.* Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48(1), 35–45 (2003).

32 Weisman MH, Moreland LW, Furst DE *et al.* Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin. Ther.* 25(6), 1700–1721 (2003).

33 Bernal Rivera L, Guerrero Aznar MD, Monzón Moreno A, Beltrán García M, Hernández Cruz B, Colmenero MA. [Effectiveness and safety of adalimumab and etanercept for rheumatoid arthritis in a third-level hospital]. *Farm. Hosp.* 30(4), 223–229 (2006).

34 De Stefano R, Frati E, Nargi F *et al.* Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide–anti-TNF-α versus methotrexate–anti-TNF-α. *Clin. Rheumatol.* 29(5), 517–524 (2010).

35 Hoff M, Kvien TK, Kalvesten J, Elden A, Kavanaugh A, Haugeberg G. Adalimumab reduces hand bone loss in rheumatoid arthritis independent of clinical response: subanalysis of the PREMIER study. *BMC Musculoskelet. Dis.* 12, 54 (2011).

36 Keystone EC, Kavanaugh A, Weinblatt ME, Patra K, Pangan AL. Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis. *J. Rheumatol.* 38(5), 855–862 (2011).

37 van der Heijde D, Breedveld FC, Kavanaugh A *et al.* Disease activity, physical function, and radiographic progression after long term therapy with adalimumab plus methotrexate: 5-year results of PREMIER. *J. Rheumatol.* 37(11), 2237–2246 (2010).

38 Blom M, Kievit W, Kuper HH *et al.* Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. *Arthritis Care Res. (Hoboken)* 62(9), 1335–1341 (2010).

39 van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. *Arthritis Care Res. (Hoboken)* 62(2), 226–234 (2010).

40 Mavragani CP, La DT, Stohl W, Crow MK. Association of the response to tumor necrosis factor antagonists with plasma type I interferon activity and interferon-β/α ratios in rheumatoid arthritis patients: a *post hoc* analysis of a predominantly Hispanic cohort. *Arthritis Rheum.* 62(2), 392–401 (2010).

41 Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J. Rheumatol.* 36(7), 1429–1441 (2009).

42 Strangfeld A, Hierse F, Kekow J *et al.* Comparative effectiveness of tumour necrosis factor α inhibitors in combination with either methotrexate or leflunomide. *Ann. Rheum. Dis.* 68(12), 1856–1862 (2009).

43 Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. *Clin. Rheumatol.* 28(4), 413–419 (2009).

44 Bazzani C, Filippini M, Caporali R *et al.* Anti-TNFα therapy in a cohort of rheumatoid arthritis patients: clinical outcomes. *Autoimmun. Rev.* 8(3), 260–265 (2009).

45 Favalli EG, Desiati F, Atzeni F *et al.* Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. *Autoimmun. Rev.* 8(3), 266–273 (2009).

46 Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)* 47(4), 507–513 (2008).

47 Bombardieri S, Ruiz AA, Fardellone P *et al.* Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 46(7), 1191–1199 (2007).

48 Nikas SN, Voulgari PV, Alamanos Y *et al.* Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. *Ann. Rheum. Dis.* 65(2), 257–260 (2006).

49 Wick MC, Ernestam S, Lindblad S, Bratt J, Klareskog L, Van Vollenhoven RF. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. *Scand. J. Rheumatol.* 34(5), 353–358 (2005).

50 Virkki LM, Valleala H, Takakubo Y *et al.* Outcomes of switching anti-TNF drugs in rheumatoid arthritis – a study based on observational data from the Finnish Register of Biological Treatment (ROB–FIN). *Clin. Rheumatol.* 30(11), 1447–1454 (2011).

51 Canhao H, Rodrigues AM, Mourao AF *et al.* Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. *Rheumatology (Oxford)* 51(11), 2020–2026 (2012).

52 Greenberg JD, Reed G, Decktor D *et al.* A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Ann. Rheum. Dis.* 71(7), 1134–1142 (2012).

53 Hjardem E, Ostergaard M, Podenphant J *et al.* Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor α inhibitor? *Ann. Rheum. Dis.* 66(9), 1184–1189 (2007).

▪▪ **One of a number of articles reporting data on a nationwide Danish database. Their evidence suggests that for those patients who have an inadequate response to infliximab there is clinical benefit with the use of adalimumab or etanercept.**

54 Kievit W, Adang EM, Fransen J *et al.* The effectiveness and medication costs of three anti-tumour necrosis factor α agents in the treatment of rheumatoid arthritis from prospective clinical practice data. *Ann. Rheum. Dis.* 67(9), 1229–1234 (2008).

55 Ornbjerg LM, Ostergaard M, Boyesen P *et al.* Impact of tumour necrosis factor inhibitor treatment on radiographic progression in rheumatoid arthritis patients in clinical practice: results from the nationwide Danish DANBIO registry. *Ann. Rheum. Dis.* 72(1), 57–63 (2012).

56 Gallego-Galisteo M, Villa-Rubio A, Alegre-del Rey E, Márquez-Fernández E, Ramos-Báez JJ. Indirect comparison of biological treatments in refractory rheumatoid arthritis. *J. Clin. Pharm. Ther.* 37(3), 301–307 (2012).

57 Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. *Pharmacotherapy* 31(1), 39–51 (2011).

58 Liu GG. Traumatic rupture of trachea and major bronchus. *Zhonghua Jie He He Hu Xi Za Zhi* 14(4), 228–230, 256 (1991).

59 Singh JA, Christensen R, Wells GA *et al.* A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 181(11), 787–796 (2009).

▪ **First network meta-analysis reporting indirect comparison of biologic DMARDs.**

60 Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. *Semin. Arthritis Rheum.* 39(6), 425–441 (2010).

61 Lee YH, Woo JH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. *Rheumatol. Int.* 28(6), 553–559 (2008).

62 Chen YF, Jobanputra P, Barton P *et al.* A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost–effectiveness. *Health Technol. Assess.* 10(42), iii–iv, xi–xiii, 1–229 (2006).

▪▪ **Government report that found that the combination of any TNF-α inhibitor with methotrexate was more effective than methotrexate alone in early rheumatoid arthritis. The study also included an economic evaluation. TNF-α inhibitors were more cost effective when used as a second choice.**

63 Heiberg MS, Rodevand E, Mikkelsen K *et al.* Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. *Ann. Rheum. Dis.* 65(10), 1379–1383 (2006).

64 Pascual-Salcedo D, Plasencia C, Ramiro S *et al.* Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology (Oxford)* 50(8), 1445–1452 (2011).

65 Alawadhi A, Alawneh K, Alzahrani ZA. The effect of neutralizing antibodies on the sustainable efficacy of biologic therapies: what's in it for African and Middle Eastern rheumatologists. *Clin. Rheumatol.* 31(9), 1281–1287 (2012).

66 Radstake TR, Svenson M, Eijsbouts AM *et al.* Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. *Ann. Rheum. Dis.* 68(11), 1739–1745 (2009).

67 Emi Aikawa N, de Carvalho JF, Artur Almeida Silva C, Bonfá E. Immunogenicity of anti-TNF-α agents in autoimmune diseases. *Clin. Rev. All. Immunol.* 38(2–3), 82–89 (2010).

68 Bartelds GM, Wijbrandts CA, Nurmohamed MT *et al.* Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann. Rheum. Dis.* 66(7), 921–926 (2007).

69 Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann. Rheum. Dis.* 71(11), 1914–1915 (2012).

70 Markenson JA, Gibofsky A, Palmer WR *et al.* Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. *J. Rheumatol.* 38(7), 1273–1281 (2011).

71 Marchesoni A, Zaccara E, Gorla R *et al.* TNF-α antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. *Ann. NY Acad. Sci.* 1173, 837–846 (2009).

72 Iannone F, Gremese E, Atzeni F *et al.* Longterm retention of tumor necrosis factor-α inhibitor therapy in a large italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J. Rheumatol.* 39(6), 1179–1184 (2012).

73 Markatseli TE, Alamanos Y, Saougou I, Voulgari PV, Drosos AA. Survival of TNF-α antagonists in rheumatoid arthritis: a long-term study. *Clin. Exp. Rheumatol.* 30(1), 31–38 (2012).

74 Burmester GR, Panaccione R, Gordon KB, Mcilraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann. Rheum. Dis.* 72(4), 517–524 (2013).

75 Schiff MH, Burmester GR, Kent JD *et al.* Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 65(7), 889–894 (2006).

76 Burmester GR, Mease P, Dijkmans BA *et al.* Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann. Rheum. Dis.* 68(12), 1863–1869 (2009).

77 Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum.* 56(9), 2896–2904 (2007).

78 Atzeni F, Sarzi-Puttini P, Botsios C *et al.* Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. *Autoimmun. Rev.* 12(2), 225–229 (2012).

79 Curtis JR, Xie F, Chen L *et al.* The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. *Ann. Rheum. Dis.* 70(8), 1401–1406 (2011).

80 Pena-Sagredo JL, Hernandez MV, Fernandez-Llanio N *et al.* Listeria monocytogenes infection in patients with rheumatic diseases on TNF-α antagonist therapy: the Spanish Study Group experience. *Clin. Exp. Rheumatol.* 26(5), 854–859 (2008).

81 Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.* 57(5), 756–761 (2007).

82 Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V *et al.* Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 52(6), 1766–1772 (2005).

83 Theophile H, Schaeverbeke T, Miremont-Salame G *et al.* Sources of information on lymphoma associated with anti-tumour necrosis factor agents: comparison of published case reports and cases reported to the French pharmacovigilance system. *Drug Saf.* 34(7), 577–585 (2011).

84 Salmon-Ceron D, Tubach F, Lortholary O *et al.* Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving

anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann. Rheum. Dis.* 70(4), 616–623 (2011).

85 Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology (Oxford)* 50(1), 222–229 (2011).

86 Dixon WG, Hyrich KL, Watson KD *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann. Rheum. Dis.* 69(3), 522–528 (2010).

87 Tubach F, Salmon D, Ravaud P *et al.* Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research axed on tolerance of biotherapies registry. *Arthritis Rheum.* 60(7), 1884–1894 (2009).

88 Strangfeld A, Listing J, Herzer P *et al.* Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-α agents. *JAMA* 301(7), 737–744 (2009).

89 Galloway JB, Mercer LK, Moseley A *et al.* Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 72(2), 229–234 (2012).

90 Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum.* 50(6), 1740–1751 (2004).

91 Askling J, van Vollenhoven RF, Granath F *et al.* Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor α therapies: does the risk change with the time since start of treatment? *Arthritis Rheum.* 60(11), 3180–3189 (2009).

92 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 295(19), 2275–2285 (2006).

93 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum.* 56(9), 2886–2895 (2007).

94 Setoguchi S, Solomon DH, Weinblatt ME *et al.* Tumor necrosis factor α antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum.* 54(9), 2757–2764 (2006).

95 Chakravarty EF, Farmer ER. Risk of skin cancer in the drug treatment of rheumatoid arthritis. *Expert Opin. Drug Saf.* 7(5), 539–546 (2008).

96 Amari W, Zeringue AL, McDonald JR, Caplan L, Eisen SA, Ranganathan P. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. *Rheumatology (Oxford)* 50(8), 1431–1439 (2011).

97 Lopez-Olivo M, Tayar J, Martinez-Lopez J *et al.* Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy. A meta-analysis. *JAMA* 308(9), 898–908 (2012).

98 van Schouwenburg PA, Bartelds GM, Hart MH, Aarden L, Wolbink GJ, Wouters D. A novel method for the detection of antibodies to adalimumab in the presence of drug reveals 'hidden' immunogenicity in rheumatoid arthritis patients. *J. Immunol. Methods* 362(1, 2), 82–88 (2010).

99 Vesga L, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. *Gut* 54(6), 890 (2005).

100 Mishkin DS, Van Deinse W, Becker JM, Farraye FA. Successful use of adalimumab (Humira) for Crohn's disease in pregnancy. *Inflamm. Bowel Dis.* 12(8), 827–828 (2006).

101 Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)- α therapy. *Rheumatology (Oxford)* 46(4), 695–698 (2007).

102 Cush JJ. Biological drug use: US perspectives on indications and monitoring. *Ann. Rheum. Dis.* 64(Suppl. 4), 18–23 (2005).

103 Johnson D, Jones K, Jimenez J *et al.* Pregnancy outcomes in women exposed to adalimumab: an update on the Autoimmune Diseases in Pregnancy Project Abstract Presented at: *The American College of Gastroenterology 2009 Annual Scientific Meeting.* San Diego, CA, USA, 23–28 October 2009.

104 Orozco C, Dao K, Cush JJ, Kavanaugh A. Safety of TNF inhibitors during pregnancy in patients with inflammatory arthritis [abstract]. *Arthritis Rheum.* 52(Suppl. 1), 22–23 (2005).

105 Verstappen SM, King Y, Watson KD, Symmons DP, Hyrich KL. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 70(5), 823–826 (2011).

106 Ostergaard M, Baslund B, Rigby W *et al.* Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, Phase I/II study. *Arthritis Rheum.* 62(8), 2227–2238 (2010).

107 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.* 70(12), 2119–2125 (2011).

108 Fridman JS, Scherle PA, Collins R *et al.* Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J. Immunol.* 184(9), 5298–5307 (2010).

109 West K. CP-690550, a JAK3 inhibitor as an immunosuppressant for the treatment of rheumatoid arthritis, transplant rejection, psoriasis and other immune-mediated disorders. *Curr. Opin. Invest. Drugs* 10(5), 491–504 (2009).

110 Landewe R. Predictive markers in rapidly progressing rheumatoid arthritis. *J. Rheumatol. Suppl.* 80, 8–15 (2007).

111 Vazquez I, Graell E, Gratacos J *et al.* Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. *Clin. Exp. Rheumatol.* 25(2), 231–238 (2007).

Websites

201 NICE: the management of rheumatoid arthritis in adults (clinical guideline 79). www.nice.org.uk/CG79

202 EMA: Humira® (adalimumab). EPAR – Scientific Discussion. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000481/WC500050867.pdf

203 US FDA. Clinical pharmacology and biopharmaceutics review(s). Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Application 12505/0 (2004). www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm092770.pdf

204 EMA. Annex I: Summary Of Product Characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf