Drugs of the Future 2001, 26(7): 639-646

CCC: 0377-8282/2001

Adalimumab

Prop INN

Antiarthritic
Treatment of IBD

D2E7

Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7 κ-chain, dimer

CAS: 331731-18-1
EN: 255014

Introduction

Rheumatoid arthritis is a chronic disease of unknown etiology that affects 1% of all Americans and 7% of the worldwide population (1, 2). The disease is three times more common in women and the peak age of onset is 25-45 years; only 10-15% of new cases occur in the elderly (1, 3, 4). The disease is characterized by persistent autoimmune activity manifesting as symmetrical joint pain, inflammation, local injury of bone and cartilage and pannus formation. Pain, stiffness, warmth, redness and swelling are experienced due to inflammation of the membranes lining the joints, especially the distal small joints in the hands, wrist and feet. Other manifestations and symptoms may also occur and they include ocular inflammation, vasculitis, appearance of rheumatoid nodules, cardiopulmonary disease, neurological dysfunction, splenomegaly, fever, fatigue, loss of appetite and anemia (1).

As of yet, no single cause can be attributed to rheumatoid arthritis and it is probable that both genetic and environmental factors are involved in the risk and development of the disease. Mutations in the MHC alleles, HLA-DR1 and HLA-DR4, may increase susceptibility and contribute to progression of rheumatoid arthritis. The chronic inflammation that characterizes the disease can be due to inappropriate T-cell activation, cytokine modulation and/or membrane protein signaling. It is believed that the cascade leading to the development of rheumatoid arthritis is initiated when antigenic peptides present in the groove of the HLA-DR4 antigen, resulting in stimulation of CD4+ T cells. These T cells in turn activate macrophages, B cells and synovial fibroblasts via direct cell-to-cell interaction and cytokines (*e.g.*, activated macrophages release IL-1β and TNF-α) and rheumatoid factors secreted by B cells. These factors form immune complexes that activate complement and thus are responsible for inflammation. Joint destruction is due to the matrix metalloproteinases (MMPs) secreted by macrophages and synovial fibroblasts (1).

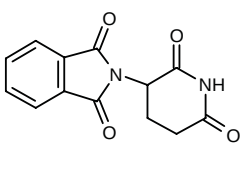
At present, treatment of rheumatoid arthritis which may be pharmacological or surgical attempts to maintain function, reduce pain and prevent irreversible joint damage. Typical pharmacological interventions generally involve administration of NSAIDs and disease modifying antirheumatic drugs (DMARDs). However, although NSAIDs reduce pain and inflammation and improve mobility, they do not influence the progression of damage to joints. DMARDs (*e.g.*, leflunomide), on the other hand, have been shown to have a significant effect on morbidity and mortality in patients with rheumatoid arthritis. At first, these agents were thought to be ineffective against pain. However, studies have suggested that DMARDs can control both pain and progression of disability even more effectively than NSAIDs. However, the long-term tolerability and efficacy with DMARDs appears to be limited and the effects of these agents on articular, functional and radiographic outcomes in patients with rheumatoid arthritis have not been shown (1, 5). The consequence has been concentrating on the development of immune system-targeted therapies as an alterative. The various components of the immune system involved in the initiation and progression of rheumatoid arthritis (*e.g.*, cytokines, chemokines, T cells, B cells, monocytes, fibroblasts, dendritic cells, mast cells, neutrophils and adhesion molecules) are all potential targets of immunomodulatory therapy for rheumatoid arthritis. In particular, cytokine therapy appears to be very promising. Rheumatoid arthritis has been considered a disorder of cytokine dysregulation where the activity of proinflammatory cytokines increases suppressing the action of those cytokines with antiinflammatory activity (6). Thus, research has focused on development of agents to neutralize proinflammatory cytokines such as IFN-γ, IL-1, IL-2, IL-6 and TNF-α (and possibly IL-15, IL-17 and IL-18) which are produced by activated T cells in the synovium during the early stages of rheumatoid arthritis (1).

The proinflammatory, pleiotropic cytokine TNF-α has been identified as having major pathological significance in the development and progression of rheumatoid

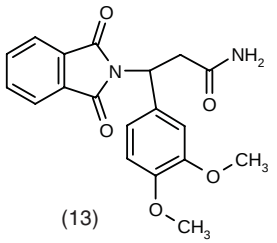
L.A. Sorbera, X. Rabasseda, R.M. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Table I: TNF-α antagonists and TNF-α production inhibitors in development for rheumatoid arthritis (Prous Science Drug R&D Backgrounders database).

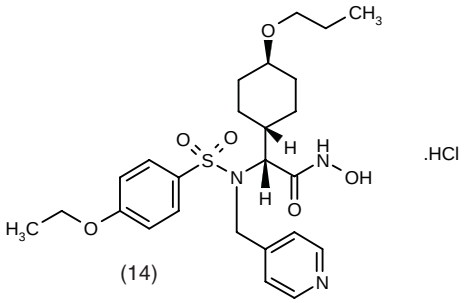
Drug Name	Company	Mechanism of Action	Status
1. Etanercept (*Enbrel*)	Immunex/Wyeth-Ayerst	Soluble TNFR:Fc fusion protein, TNF-α antagonist	Launched-1998
2. Infliximab (*Remicade*)	Centocor	Humanized anti-TNF-α antibody	Launched-1998
3. Adalimumab	Cambridge Antibody Technol./Abbott/Eisai	Recombinant human anti-TNF-α antibody	Phase III
4. CDP-870	Celltech/Pharmacia	Pegylated recombinant human anti-TNF-α antibody	Phase II
5. DPC-333*	Dupont Pharm.	TNF-α converting enzyme (TACE) inhibitor	Phase II
6. PEG-sTNF-RI	Amgen	Pegylated soluble TNFR, TNF-α antagonist	Phase II
7. rhTBP-1	Serono	Recombinant human TNF binding protein type 1	Phase II
8. Thalidomide	Andrulis/Celgene	TNF-α production inhibitor and angiogenesis inhibitor	Phase II
9. AGIX-4207*	AtheroGenics	Selective TNF-α modulator	Phase I
10. CC-1088*	Celgene	TNF-α production inhibitor, thalidomide analog	Phase I
11. CLX-0921+,*	Calyx Therapeutics	TNF-α production inhibitor	Phase I
12. ISIS-104838	Isis/Elan	Antisense oligonucleotide, inhibitor of TNF-α expression	Phase I
13. CC-1069	Celgene	TNF-α and IL-2 production inhibitor, thalidomide analog	Preclinical
14. CGS-33090A	Novartis	TNF-α release inhibitor and MMP inhibitor	Preclinical
15. CLX-120500+,*	Calyx Therapeutics	TNF-α antagonist and TNF-α production inhibitor	Preclinical
16. GW-4459	GlaxoSmithKline	TNF-α converting enzyme (TACE) inhibitor and MMP inhibitor	Preclinical
17. TTL-3	Nereus	TNF-α production inhibitor	Preclinical
18. Y-39041	Welfide	TNF-α production inhibitor and IL-10 production enhancer	Preclinical



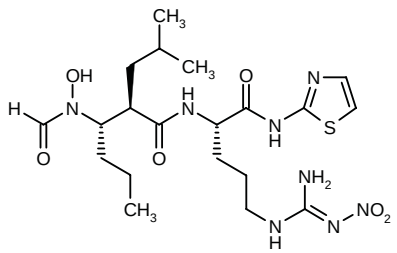
(8)



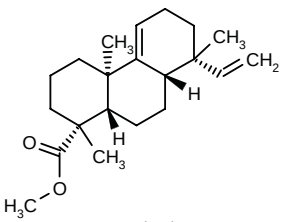
(13)



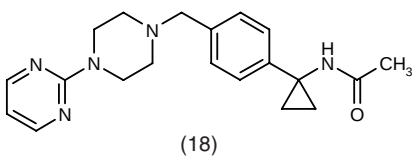
(14)



(16)



(17)



(18)

+Also COX-2 expression inhibitor. *Structure not yet detected.

arthritis and other inflammatory autoimmune diseases. TNF-α is overproduced in patients with rheumatoid arthritis and has been identified in the synovial membrane especially at the cartilage-pannus junction of these patients. Its presence has been associated with more severe cases of the disease. TNF-α is involved in joint destruction since it can stimulate bone and cartilage resorption, induce inflammation and inhibit bone formation by suppressing bone collagen synthesis and it has also been implicated as the cause of fatigue, malaise, fever, anemia and cachexia in patients with rheumatoid arthritis (1, 7-9). Thus, inhibition of TNF-α production or blockade of the interaction of TNF-α with its receptors is the focus of research for the development of therapies for rheumatoid arthritis. TNF-α antagonists and TNF-α production inhibitors currently under development for rheumatoid arthritis are shown in Table I. One such next-generation anti-TNF-α agent that has shown promise is adalimumab (D2E7). It is a fully human anti-TNF-α antibody that binds to and neutralizes TNF-α, thus interrupting inflammatory responses. It has no non-human or artificially fused human sequences and therefore has a greater potential for low immunogenicity and higher therapeutic efficacy. Adalimumab was chosen for further development as a treatment for rheumatoid arthritis.

Pharmacological Actions

Adalimumab was shown to bind to the human TNF receptor with a fast on rate (1.9×10^5 $M^{-1}s^{-1}$) and a slow off rate (8.8×10^{-5} s^{-1}). The agent inhibited binding of human TNF to its receptor on human U937 cells with an IC_{50} value of 0.16 nM. Similar binding affinity was exhibited by the agent for p55 and p75 TNF receptors. Adalimumab was also shown to neutralize TNF bioactivity in several in vitro models. The agent inhibited human TNF-induced cytotoxicity in murine L929 cells (IC_{50} = 0.13 nM) and expression of endothelial leukocyte adhesion molecule (ELAM-1) in human umbilical vein endothelial cells (HUVEC) following activation with human TNF (IC_{50} = 0.19 nM). The agent was also shown to bind to pro-TNF on cell membranes to mediate complement-dependent cytotoxicity and to Fc receptors on human cells to mediate antibody-dependent cell cytotoxicity (10).

The immunomodulatory activity of adalimumab was also demonstrated in a number of *in vitro* models. The agent protected mice from lethality due to administration of human TNF in combination with galactosamine (ED_{50} = 1-2.6 μg/mouse) and dose-dependently inhibited human TNF-induced pyrexia in rabbits (10). Moreover, adalimumab (1 and 10 mg/kg i.p. once weekly for 9 weeks starting when mice were 1 week old) prevented the development of polyarthritis in human TNF transgenic mice (Tg197). In contrast to control mice that showed clinical signs of arthritis at 4 weeks of age which progressed to severe arthritis at 9 weeks of age, adalimumab-treated mice exhibited a dose-dependent and marked inhibition of arthritis parameters at all time points (ED_{50} = 0.3-0.5 mg/kg). The mean clinical arthritis scores for animals treated with 1 and 10 mg/kg adalimumab were 0.4 ± 0.4 and 0.3 ± 0.3, respectively, as compared to 2.8 ± 0.7 in controls. Histological scores assessing synovial thickening, pannus formation, cartilage degradation and bone erosion (0-3) for animals treated with the 1 and 10 mg/kg doses were 0 as compared to 2.9 ± 0.2 in controls. While low doses of 0.01 and 0.1 mg/kg adalimumab had no effect on arthritis severity, the 0.5 mg/kg dose resulted in partial protection from arthritis progression (11).

Adalimumab (200 μg/mouse i.v. once weekly for 4 weeks), however, was ineffective in significantly influencing cartilage invasion and angiogenesis in fresh synovial and cartilage tissues taken from 8 patients with rheumatoid arthritis undergoing joint replacement and engrafted s.c. on SCID/bg mice. Cartilage invasion scores, perichondrocytic resorption and numbers of blood vessels or T cells in synovial tissue were similar in both control and treated animals (12).

Two methods have been developed for routine analysis of adalimumab and identification of its isoforms. The cation-exchange liquid chromatography (CIEX) and capillary isoelectric focusing (cIEF) methods described were capable of separating the heavy chain C-terminal variants of adalimumab and the enzymatic digestion procedures devised allowed for identification of C-terminal lysine variants. (13).

Clinical Studies

Results from a single-dose, placebo-controlled phase I study conducted in 50 patients with active rheumatoid arthritis examined the short-term efficacy and influence of adalimumab (0.5, 1 or 10 mg/kg for 14 days). Synovial knee biopsies were obtained from 25 patients on days 0 and 14. Treatment with the agent resulted in rapid and significant clinical improvement as measured by the composite disease activity (DAS) score on day 14 as compared to day 1 and a significant decrease in acute phase parameters (*i.e.*, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). Although TNF-α mRNA levels were unaffected, treatment significantly reduced the peripheral blood levels of IL-1beta mRNA and circulating IL-6, and IL-1 receptor endogenous antagonists decreased below baseline within 24 h of dosing where they were maintained for up to 14 days; TNF receptor levels significantly decreased by day 14. Although clinical improvement was observed in adalimumab-treated patients, immunohistological changes at the synovial level were not consistent. Endothelial IL-1β staining only tended (p = 0.06) to decrease although this was not observed in responders. Levels of staining for endothelial IL-1β and TNF-α in sublining layers and vessels of treated patients correlated with microscopic inflammation scores although results did not reach significance (14).

Treatment with adalimumab had no effect on activity of the hypothalamic-pituitary-adrenal (HPA)-axis according to analysis of 7 patients with active rheumatoid arthritis treated with a single i.v. dose of the agent and compared to 9 patients participating in another study who received either placebo or Ro-45-2081. DAS was significantly improved in the treated groups as compared to placebo (mean decrease of 0.64 ± 0.46 *vs.* 0.09 ± 0.35 in placebo). No changes in plasma ACTH, plasma or urinary cortisol or circadian cortisol rhythm were observed with treatment (15).

Results from a study examining polymorphonuclear cells (PMN) from the blood of 25 patients with active rheumatoid arthritis and 25 matched controls 14 days after administration of single-dose adalimumab or placebo showed that treatment with the agent did not impair PMN function. Treatment with the agent corrected for the increased levels of PMA-stimulated reactive oxygen species (ROS) production seen in rheumatoid arthritis patients but ROS levels were not reduced to levels below normal. Treatment did not alter chemotaxis of PMN (16).

The efficacy and tolerability of s.c. adalimumab (0.5 mg/kg once weekly for up to 6 months) was shown in a double-blind, phase I trial involving 24 patients with active rheumatoid arthritis. The ongoing study included a subsequent open-label phase including all 24 patients (nonresponders or patients losing their responder status received 1 mg/kg adalimumab s.c.). A good local tolerability profile was obtained following 300 s.c. injections. Only 1 patient (72 years old) on placebo discontinued for myocardial infarction. Plasma concentrations of s.c. administrated adalimumab were comparable to levels

Box 1: Long-term efficacy and tolerability of adalimumab in patients with rheumatoid arthritis (19) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with active RA who have failed a mean of 3.9 DMARD treatments (n = 120)
Treatments[+]	Adalimumab, 0.5 mg/kg i.v. Adalimumab, 1 mg/kg i.v. Adalimumab, 3 mg/kg i.v. Adalimumab, 5 mg/kg i.v. Adalimumab, 10 mg/kg i.v. Placebo
Withdrawals	A: 12/120 (10.0%) [lack of efficacy 6/120 (5.0%), adverse events 5/120 (4.2%), patient request 1/120 (0.8%)]
Results	Rate of patients achieving and sustaining response status (drop of 1.2 in DAS value) (%) @ 12 mo: A (80) SJC score, change @ 12 mo: A (–60%) TJC score, change @ 12 mo: A (–60%)
Conclusions	Adalimumab was safe and effective in active rheumatoid arthritis

[+]Adalimumab was administered 1x/2.5 wks [mean] x 12 mo

seen following i.v. administration of the agent. After 2 months, treated patients exhibited a mean reduction in DAS, swollen joint counts (SJC) and tender joint counts (TJC) of approximately 50, 60 and 70%, respectively (17).

The efficacy of adalimumab (0.5, 1, 3, 5 and 10 mg/kg i.v. over 3-5 min) was demonstrated in a randomized, double-blind, placebo-controlled, single-dose phase I trial involving 120 patients with active rheumatoid arthritis (mean disease duration = 11.5 years; mean duration of DMARD pretreatment = 3.9 years). Treatment was well tolerated with no clinically significant drug-related adverse events seen. Preliminary pharmacokinetic analysis from 89 patients revealed that AUC increased proportionally with dose. The mean total serum clearance of the agent was 0.18-0.271 ml/min and the steady-state volume of distribution was 0.063-0.076 l/kg. A terminal $t_{1/2}$ of 11.6-13.7 days was estimated for the agent. Clinical improvements were observed 24 h after the first dose and peaked at weeks 1-2. Response status (*i.e.*, a decrease in baseline DAS of 1.2 or greater) was achieved in 41, 72, 67, 56 and 78% of the patients receiving the respective adalimumab doses as compared 19% on placebo; responses were observed for up to 12 weeks. On day 29 postdosing, response rates were 6, 28, 33, 44 and 39%, respectively, as compared to 0% on placebo. All patients continued in a subsequent open-label phase of the study to examine the long-term efficacy and tolerability of multiple-dose i.v. adalimumab (every 2 weeks until a good response was achieved according to EULAR [European League Against Rheumatism] response criteria). In this study, adalimumab was concluded to be generally well tolerated after more than 1400 doses were administered for up to 12 months. At the time of reporting, 12 patients had discontinued the open-label phase for lack of efficacy (6 patients), pneumonia (1 patient), myalgia (1 patient), allergies (2 patients), pancreatitis (1 patient) and patient request (1 patient). Responder status was achieved and sustained in more than 80% of the patients by 12 months. A 60% decrease in SJC and TJC was also seen in these responders (18, 19) (Box 1).

The long-term efficacy of adalimumab (20, 40 or 80 mg s.c. self-injection for up to 6 months) was demonstrated in a randomized, double-blind, placebo-controlled, dose-finding, trial conducted in 283 patients with active rheumatoid arthritis (mean duration of disease = 8 years; TJC = 30; SJC = 18; ESR = 45 mm/h; CRP = 5.1 mg/dl; 4 previous DMARDs). After 3 and 6 months, significantly more patients receiving the 20, 40 and 80 mg doses achieved an ACR 20 response (American College of Rheumatology improvement criteria) as compared to placebo (49, 57 and 56% at 3 months, respectively, and 56, 64 and 63%, at 6 months, respectively, vs. 10% in placebo). In addition, significantly more treated patients exhibited improvements in TJC, SJC and CRP as compared to placebo. The three adalimumab doses resulted in stable and comparable efficacy parameters over the treatment period (20, 21) (Box 2).

Long-term treatment with adalimumab (0.5-10 mg/kg i.v. every 2 weeks for 1 year) was shown to slow radiographic disease progression in a study analyzing the complete x-rays of the hands, wrists and feet of 66 patients with active rheumatoid arthritis taken at baseline and 6 and 12 months and 22 additional patients with available prestudy (about –19 months) x-rays. No radiographic disease progression was observed following adalimumab treatment compared to deterioration observed during previous DMARD treatment (22).

The disease activity of 39 patients with refractory rheumatoid arthritis was assessed during long-term adalimumab treatment (3, 5 or 10 mg/kg i.v.). Patients were administered the agent following a dose-escalation phase and redosed to adjust therapy to disease activity only if they had a DAS above 2.4. Patients were evaluated biweekly for 1 year of follow-up. Within the first 4 weeks, 78% of the patients achieved ACR 20. The mean DAS decreased from 5.11 to 3.61 at 3 months and was sustained. Only 48 and 15% of the patients achieved a DAS

Box 2: Efficacy of adalimumab in active rheumatoid arthritis (21) [Prous Science Integrity database].

Design	Randomized, double-blind, dose-finding, crossover, placebo-controlled clinical study
Population	Patients with long-standing active RA (n = 283)
Treatments	Adalimumab, 20 mg s.c. 1x/wk x 6 mo Adalimumab, 40 mg s.c. 1x/wk x 6 mo Adalimumab, 80 mg s.c. 1x/wk x 6 mo Placebo x 3 mo → Adalimumab, 40 mg s.c. 1x/wk x 3 mo
Results	ACR 20 response @ 3 mo: A40 (57) ≥ A80 (56) ≥ A20 (49) > P (10); @ 6 mo: A40 (64) ≥ A80 (63) ≥ P → A40 (59) ≥ A20 (56) TJC 30 response @ 3 mo: A20 (61) ≥ A40 (57) ≥ A80 (55) > P (5); @ 6 mo: A20 (69) ≥ A40 (63) = A80 (63) ≥ P → A40 (55) SJC 18 response @ 3 mo: A80 (61) ≥ A40 (59) ≥ A20 (42) > P (16); @ 6 mo: A40 (68) ≥ A80 (62) ≥ P → A40 (56) ≥ A80 (54) Median CRP response @ 3 mo: A40 (67) ≥ A80 (64) ≥ A20 (54) > P (1); @ 6 mo: P → A40 (67) ≥ A80 (66) ≥ A20 (59) ≥ A40 (58)
Conclusions	Adalimumab was effective in long-standing active rheumatoid arthritis. Doses of 20, 40 and 80 mg/wk showed similar efficacy

Box 3: Efficacy of monotherapy with adalimumab versus methotrexate in rheumatoid arthritis (25) [Prous Science Integrity database].

Design	Comparative clinical study
Population	Patients with active RA (n = 198)
Treatments	Adalimumab x 48 wks (n = 61) Methotrexate x 48 wks (n = 137)
Withdrawals	A: 23% M: 45%
Results	Risk of dropout (uncorrected RR) @ 48 wks: A (0.28) Risk of dropout (corrected RR) @ 48 wks: A (0.17) $DAS_{0\text{-}48}$ AUC @ 48 wks: M > A [p = 0.005] Response rate @ 48 wks: A > M Median rate of visits in which a patient fulfilled the EULAR response criteria: A (83) > M (40) [p = 0.0001] Probability of prolonged efficacy in responder patients after the first dose (RR): A (2) Probability of response in patients with previous DMARDs (RR): M (–0.71)
Conclusions	Adalimumab was more effective and safer than methotrexate in long-standing active rheumatoid arthritis

below 2.4 and 1.6, respectively. Results indicate a discrepancy between dichotomous response percentages (ACR) and long-term DAS. DAS was concluded to be more effective in daily clinical practice enabling facility of individual dose titrations as opposed to determination of long-term efficacy (23).

A long-term efficacy of up to 2 years was demonstrated for adalimumab in a study conducted in 24 patients with active rheumatoid arthritis who had previously failed a mean of 3.5 DMARDs (mean disease duration = 10 years; mean DAS = 5.35). The study included a randomized, double-blind, placebo-controlled, 12-week phase followed by an open-label phase for up to 2 years. Patients received adalimumab for up to 2 years at a dose of 0.5 mg/kg s.c. weekly or 1 mg/kg s.c. weekly if they did not achieve a EULAR response by week 8 (2 patients) or if previously on placebo in the double-blind phase (5 patients). Treatment was well tolerated with a comparable adverse event profile for both placebo and adalimumab groups. At 2 years, EULAR, ACR 20 and ACR 50 responses were achieved in 74, 64 and 35% of the treated patients, respectively. DAS decreased from a mean of 5.23 at baseline to 2.60. Improvements in the Ritchie Index (4 *vs.* 18), SJC (2 *vs.* 20 at baseline) and CRP (11.8 *vs.* 35 mg/ml at baseline) were also observed at 2 years (24).

The efficacy of adalimumab was compared to methotrexate (MTX) monotherapy in patients with active rheumatoid arthritis with results showing that adalimumab was more effective and better tolerated. Results from 61 patients enrolled in phase I trials, administered adalimumab and followed for 48 weeks or more, were compared to results from 137 patients on MTX monotherapy participating in a 48-week phase III study. Adalimumab-treated patients had a significantly longer disease duration (108 *vs.* 50 months) and used more previous DMARDs (4 *vs.* 1) as compared to the MTX group. Significantly more adalimumab patients achieved a EULAR response as compared to MTX (83 *vs.* 40%). Further randomized studies were initiated to better determine the efficacy of adalimumab over MTX (25) (Box 3).

Box 4: Safety and efficacy of combination therapy with adalimumab and methotrexate in rheumatoid arthritis (26) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with active RA despite standard doses of methotrexate (n = 54)
Treatments	Methotrexate, 16 mg [mean] 1x/wk + Adalimumab, 1 mg i.v. → Methotrexate, 16 mg [mean] 1x/wk + Adalimumab, 1 mg s.c. x 2 y (n = 18) Methotrexate, 16 mg [mean] 1x/wk + Adalimumab, 1 mg s.c. → Methotrexate, 16 mg [mean] 1x/wk + Adalimumab, 1 mg s.c. x 2 y (n = 18) Methotrexate, 16 mg [mean] 1x/wk + Placebo → Methotrexate, 16 mg [mean] 1x/wk + Adalimumab, 1 mg s.c. x 2 y (n = 18)
Withdrawals	Adverse events 6/54 (11.1%), lack of efficacy 2/54 (3.7%), death 1/54 (1.9%), protocol violation 1/54 (1.9%)
Results	EULAR response rate (%) @ 6 mo: A (87); @ 12 mo: A (85); @ 18 mo: A (80); @ 24 mo: A (78) ACR 20 response rate (%) @ 6 mo: A (72); @ 12 mo: A (63); @ 18 mo: A (63); @ 24 mo: A (50) ACR 50 response rate (%) @ 6 mo: A (30); @ 12 mo: A (28); @ 18 mo: A (43); @ 24 mo: A (30) Median DAS, at baseline: A (4.7); @ 6 mo: A (2.9); @ 12 mo: A (3.0); @ 18 mo: A (2.5); @ 24 mo: A (2.6) Median Ritchie index, at baseline: A (16.0); @ 6 mo: A (6.0); @ 12 mo: A (7.0); @ 18 mo: A (4.5); @ 24 mo: A (4.5) Median SJC [0-44 joints], at baseline: A (19); @ 6 mo: A (7.0); @ 12 mo: A (8.0); @ 18 mo: A (6.0); @ 24 mo: A (4.5)
Conclusions	Adalimumab in combination with methotrexate was well tolerated and effective in active rheumatoid arthritis

Box 5: Efficacy of combination therapy with adalimumab and methotrexate in rheumatoid arthritis (29) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with active refractory RA despite methotrexate (n = 271)
Treatments	Methotrexate, 16.8 mg/wk [mean] x 24 wks + Adalimumab, 20 mg s.c. 1x/2wk x 24 wks Methotrexate, 16.8 mg/wk [mean] x 24 wks + Adalimumab, 40 mg s.c. 1x/2wk x 24 wks Methotrexate, 16.8 mg/wk [mean] x 24 wks + Adalimumab, 80 mg s.c. 1x/2wk x 24 wks Methotrexate, 16.8 mg/wk [mean] x 24 wks + Placebo, x 24 wks
Adverse Events	A: injection site reactions 14.8% P: injection site reactions 3.2%
Results	ACR 20 response rate (%) @ 24 wks: A80* (65.7) = A40* (65.7) ≥ A20* (49.3) > P (14.5) [*p <0.0001 *vs.* P] ACR 50 response rate (%) @ 24 wks: A40* (53.7) ≥ A80* (52.7) ≥ A20** (31.9) > P (8.1) [*p <0.0001 *vs.* P; **p <0.02 *vs.* P] ACR 70 response rate (%) @ 24 wks: A40* (26.9) ≥ A80* (19.2) ≥ A20 (10.1) ≥ P (4.8) [*p <0.02 *vs.* P]
Conclusions	Adalimumab in combination with methotrexate was effective in active refractory rheumatoid arthritis

The long-term efficacy and safety of adalimumab in combination with MTX was shown in a randomized, placebo-controlled study involving 54 patients with rheumatoid arthritis who were partial responders to standard doses (mean = 16 mg/week) of MTX. Patients were administered standard MTX doses and adalimumab first in a double-blind manner (1 mg/kg i.v. or s.c.) followed by a subsequent open-label phase (1 mg/kg s.c. every other week up to every other month depending on individual responses) for up to 2 years. The incidence of adverse events was similar in the combination treatment and placebo groups during the double-blind phase of the study. Forty-four patients completed the 2-year study; discontinuations were due to adverse events (6 patients), lack of efficacy (2 patients), death (1 patient) and protocol violation (1 patient). Results from the open-label phase at 2 years indicated that EULAR, ACR 20 and ACR 50 responses were achieved in 78, 50 and 30% of the treated patients, respectively. DAS decreased from a mean of 4.72 at baseline to 2.58. Improvements in the Ritchie Index (4.5 *vs.* 16) and SJC (0-44 joints; 4.5 *vs.* 19 at baseline) were also observed at 2 years (26) (Box 4).

Similar results were obtained in two other trials showing the efficacy of combination adalimumab + MTX. Results from a randomized, unblinded, 24-week study in which 59 partial responders to MTX with rheumatoid arthritis were administered adalimumab (0.25-5 mg/kg) mg/kg) in addition to MTX showed that the average clearance of MTX was only slightly increased with combination treatment. Dose-dependent $t_{1/2}$ and serum clearance values obtained were 353-464 h and 0.009-0.012 l/h, respectively. Of a total of 58 patients, ACR 20 responses

were seen after 24 weeks in 67, 71, 52, 67 and 75% of the patients receiving doses of 0.25, 0.5, 1, 3 and 5 mg/kg, respectively; the ACR 50 response rates were 50, 43, 29, 58 and 67%, respectively. Improvements in SJC and TJC were also observed (27).

The significant efficacy of adalimumab was further emphasized from results of the randomized, double-blind, placebo-controlled ARMADA trial involving 271 patients with active rheumatoid arthritis (mean disease duration = 12.3 years) despite being on stable doses (16.8 mg/week) of MTX. In this study, patients received concurrent adalimumab or placebo at doses of 20, 40 and 80 mg (s.c. every other week for 24 weeks). The 20, 40 and 80 mg adalimumab doses resulted in significantly higher ACR 20 (49.3, 65.7 and 65.7%, respectively, *vs.* 14.5% in placebo) and ACR 50 (31.9, 53.7 and 52.7%, *vs.* 8.1%) responses as compared to placebo; significantly more patients in the 40 (26.9%) and 80 (19.2%) mg dose groups achieved an ACR 70 response as compared to placebo (4.8%) and the 20 mg adalimumab groups (10.1%). Treatment was well tolerated with the majority of adverse events similar in both placebo and treatment groups. However, a higher incidence of injection reaction was seen in patients treated with adalimumab (15.2 *vs.* 3.2% in placebo) (28) (Box 5).

According to results from phase I and II trials, adalimumab was safe and significantly effective as a treatment for rheumatoid arthritis even when administered for as long as 4 years. Adalimumab is currently undergoing phase III studies in Europe and North America as a treatment for rheumatoid arthritis (29, 30).

Manufacturer

Discovered by Cambridge Antibody Technology Ltd. (GB); licensed to Knoll GmbH (DE), now part of Abbott Laboratories Inc. (US).

References

1. Prous Science Drug R&D Backgrounders: *Rheumatoid arthritis (online publication).* Updated June 20, 2001.

2. Vane, J. *Introduction.* Drugs Today 1999, 35: 223-4.

3. Shmerling, R.H. *Rheumatoid arthritis.* Drugs Today 1998, 34: 649-53.

4. Matteson, E.L. *Current treatment strategies for rheumatoid arthritis.* Mayo Clin Proc 2000, 75: 69-74.

5. Cush, J.J. *Rationale and risks of novel immunomodulatory therapies in rheumatoid arthritis.* Drugs Today 1999, 35: 287-94.

6. Kavanaugh, A. *An overview of immunomodulatory intervention in rheumatoid arthritis.* Drugs Today 1999, 35: 275-86.

7. Chu, C.Q., Field, M., Feldmann, M., Maini, R.N. *Localization of tumor necrosis factor alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis.* Arthritis Rheum 1991, 34: 1125-32.

8. Odeh, M. *Role of cytokines in rheumatoid arthritis.* Drug News Perspect 1998, 11: 331-41.

9. Williams, R.O., Feldmann, M., Maini, R.N. *Cartilage destruction and bone erosion in arthritis: The role of tumour necrosis factor α.* Ann Rheum Dis 2000, 59(Suppl. 1): i75-80.

10. Kaymakçalan, Z., Kollias, G., Haralambous, S. et al. *Development of a fully human anti-TNF monoclonal antibody.* J Interferon Cytokine Res 1998, 18: Abst 6.16.

11. Kaymakçalan, Z., Haralambous, S., Tracey, D., Kamen, R., Salfeld, J., Kollias, G. *Prevention of polyarthritis in human TNF transgenic mice by D2E7: A fully human anti-human TNF monoclonal antibody.* Arthritis Rheum 1998, 41: Abst 390.

12. Jorgensen, C., Apparailly, F., Canovas, F., Sany, J. *No effect of anti-TNF antibody treatment on cartilage invasion by end stage human rheumatoid synovial tissue in the SCID/HU model.* 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 997.

13. Santora, L.C., Krull, I.S., Grant, K. *Characterization of recombinant human monoclonal tissue necrosis factor-alpha antibody using cation-exchange HPLC and capillary isoelectric focusing.* Anal Biochem 1999, 275: 98-108.

14. Barrera, P., Joosten, L., den Broeder, A., van de Putte, L., van Riel, P., van den Berg, W. *Effect of a fully human anti-TNFα monoclonal antibody on the local and systemic expression of TNF and IL-1.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-420.

15. Eijsbouts, A., den Broeder, A., Vanden Hoogen, Laan, R., Hermus, A., Sweep, F., Sander, O., Rau, R., van de Putte, L. *The effect of anti-TNF-treatment is not mediated through the HPA-axis.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-422.

16. den Broeder, A., Wanten, G., van Riel, P., van de Putte, L., Naber, T., Barrera, P. *PMN reactive oxygen species production and chemotaxis in patients with RA treated with the fully human anti-TNFα antibody D2E7.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-423.

17. Schattenkirchner, M., Kruger, L., Sander, O., Rau, R., Kroot, E.-J., van Riel, P.L.C.M., van de Putte, L., Fenner, H., Kempeni, J., Kupper, H. *Efficacy and tolerability of weekly subcutaneous injections of the fully human anti-TNF-antibody D2E7 in patients with rheumatoid arthritis: Results of a phase I study*. 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 149.

18. van de Putte, L., van Riel, P.L.C.M., den Broeder, A., Sander, O., Rau, R., Binder, C., Kruger K., Schanttenkirchner, M., Fenner, H., Salfeld, J., Bankmann, Y., Kupper, H., Kempeni, J. *A single dose placebo controlled phase I study of the fully human anti-TNF antibody D2E7 in patients with rheumatoid arthritis.* 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 148.

19. Rau, R., Sander, O., den Broeder, A., van Riel, P.L.C.M., van de Putte, L., Kruger K., Schanttenkirchner, M., Fenner, H., Lassmann, A., Kupper, H., Kempeni, J. *Long-term efficacy and tolerability of multiple i.v. doses of the fully human anti-TNF-antibody D2E7 in patients with rheumatoid arthritis.* 62nd Annu Meet Am Coll Rheumatol (Nov 8-12, San Diego) 1998, Abst 137.

20. van de Putte, L.B.A., Rau, R., Breedveld, F.C. et al. *Efficacy of the fully human anti-TNF antibody D2E7 in rheumatoid arthritis.* 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 1977.

21. van de Putte, L.B.A., Rau, R., Breedveld, F.C. et al. *Six month efficacy of the fully human anti-TNF antibody D2E7 in*

rheumatoid arthritis. Ann Rheum Dis 2000, 59(Suppl. 1): Abst OP.056.

22. Rau, R., van de Putte, L.B.A., van Riel, P.L.C.M., den Broeder, A., Schanttenkirchner, M., Wasthuber, J., Rihl, M., Fenner, H., Kempeni, J., Kupper, H. *Long-term treatment with the fully human anti-TNF antibody D2E7 slows radiographic disease progression in rheumatoid arthritis.* 63rd Annu Meet Am Coll Rheumatol (Nov 13-17, Boston) 1999, Abst 1978.

23. den Broeder, A.A., van Gestel, A.M., van Riel, P.L.C.M. *Evaluation of the disease activity in patients with RA during long-term treatment with anti-TNF.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-421.

24. Schattenkirchner, M., Rau, R., van de Putte, L.B.A., Vallbracht, I., Herbron, G., Kroot, E.J., van Riel, P.L., Dressler, R., Compagnone, D., Kupper, H. *Long-term use of the fully human anti-TNF antibody adalimumab (D2E7) in DMARD-refractory rheumatoid arthritis.* Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst OP0083.

25. Barrera, P., den Broeder, A., van der Maas, A., van Ede, A., Kiemeney, B., Laan, R., van de Putte, L., van Riel, P. *Drug survival, efficacy and toxicity of monotherapy with a fully human anti-TNFα monoclonal antibody versus MTX in RA.* Ann Rheum Dis 2000, 59(Suppl. 1): Abst POS-419.

26. Breedveld, F.C., Allaart, C.F., Rau, R. et al. *The fully human anti-TNF antibody adalimumab (D2E7) in combination with methotrexate (MTX) in the treatment of active rheumatoid arthritis: Results of a 2-year study.* Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst OP0062.

27. Weisman, M., Keystone, E., Paulus, H., Weinblatt, M., Furst, D., Moreland, L., Velagapudi, R., Fischkoff, S., Chartash, E. *A dose escalation study designed to demonstrate the safety, tolerability and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with methotrexate (MTX) in patients with active RA.* 64th Annu Meet Am Coll Rheumatol (October 29-November 2, Philadelphia) 2000. Abst 1948.

28. Keystone, E., Weinblatt, M.E., Weisman, M., Furst, D., Paulus, H., Birbara, C., Fischkoff, S., Chartash, E.K. *The fully human anti-TNF monoclonal antibody, adalimumab (D2E7), dose ranging study: The 24-week clinical results in patients with active RA on methotrexate therapy (the ARMADA trial).* Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst OP0086.

29. Fischkoff, S.A. *Long-term use of the fully human anti-TNF antibody adalimumab (D2E7) in active rheumatoid arthritis: A safety and efficacy analysis across phase I and phase II studies.* Ryumachi 2001, 41(2): 304.

30. *D2E7: Treatment for rheumatoid arthritis.* Cambridge Antibody Technology Web Site. June 6, 2001.