

EXPERT
REVIEWS

Adalimumab for the treatment of rheumatoid arthritis

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Graduate School, Tokyo Medical
and Dental University, 1-5-45,
Yushima, Bunkyo-ku,
Tokyo, Japan
Tel.: +81 358 035 201
Fax: +81 356 840 057
miya.rheu@tmd.ac.jp

Rheumatoid arthritis (RA) is characterized by massive synovial proliferation resulting in joint destruction and deterioration in quality of life. TNF- α has been implicated in the central pathogenesis of RA, and its blockade by anti-TNF- α monoclonal antibodies (infliximab and adalimumab) and the soluble TNF- α receptor (etanercept) has caused a paradigm shift in the treatment of RA. Adalimumab can be used alone or concomitantly with methotrexate, but the combination of both is significantly superior to monotherapy with adalimumab. Adalimumab can not only ameliorate the signs and symptoms of the disease, but can also inhibit the progression of joint destruction and improve quality of life. Approximately 50% of patients with early, aggressive RA receiving combination therapy with adalimumab and methotrexate can be introduced into disease remission (disease activity score < 2.6). Adalimumab is even effective in patients with RA treated previously with other biologics. Long-term treatment with adalimumab is safe and well tolerated in patients with RA.

KEYWORDS: adalimumab • methotrexate • rheumatoid arthritis • TNF- α

Rheumatoid arthritis (RA) is characterized by the inflammation and destruction of multiple joints. It can not only hamper quality of life but can also shorten the lifespan of affected patients by causing comorbidities, such as cardiovascular diseases [1]. The pathology includes new blood-vessel formation, inflammatory cell infiltration and synovial proliferation. Abundant production of proteolytic enzymes, such as metalloprotease and inflammatory cytokines, including TNF- α and IL-6, causes cartilage breakdown and bone destruction, which lead to irreversible functional disability. In addition, chemokines produced *in situ* promote recruitment of inflammatory cells in the joints.

The ultimate goals for the treatment of RA are to prevent joint damage and restore normal life [2]. Nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) have been used widely in combination to control disease activity, without complete success. Methotrexate (MTX), a folic acid antagonist that inhibits DNA and RNA synthesis, is the most potent and most commonly prescribed DMARD, and is capable of retarding joint destruction [3,4]. Treating RA early has been recommended [5]; however, the limitations of conventional DMARDs include insufficient ability to prevent the progression of damage and deterioration of patients' physical function, as well as toxicities to liver, bone marrow and lung [6].

Overview of the market

The introduction of biologics that inhibit multiple activities of inflammatory cytokines, such as TNF- α and IL-6, has significantly altered the natural course of RA and prevented joint destruction. Of note, TNF- α -blocking agents have been shown to be remarkably effective in preventing joint damage progression. Among them, infliximab and adalimumab are both anti-human TNF- α monoclonal antibodies [7,8], and etanercept is a recombinant soluble p75 receptor for TNF- α [9]. In addition, abatacept (cytotoxic T-lymphocyte-associated antigen-4 immunoglobulin fusion protein [CTLA-4]) and rituximab (chimeric anti-CD20 monoclonal antibodies), have both been shown to be useful in patients showing resistance to TNF- α antagonists [10,11]. Furthermore, tocilizumab, a humanized anti-IL-6 receptor antibody, starting to be used widely in Japan, has shown significant efficacy in treating RA patients [12,13]. Other antihuman TNF- α monoclonal antibodies, such as golimumab and certolizumab, are currently in clinical trials globally [14,15].

Introduction to adalimumab

Adalimumab is a biologic DMARD developed through the phage-display library technique and, thus, is the first anti-TNF- α monoclonal antibody with a 100% human peptide sequence

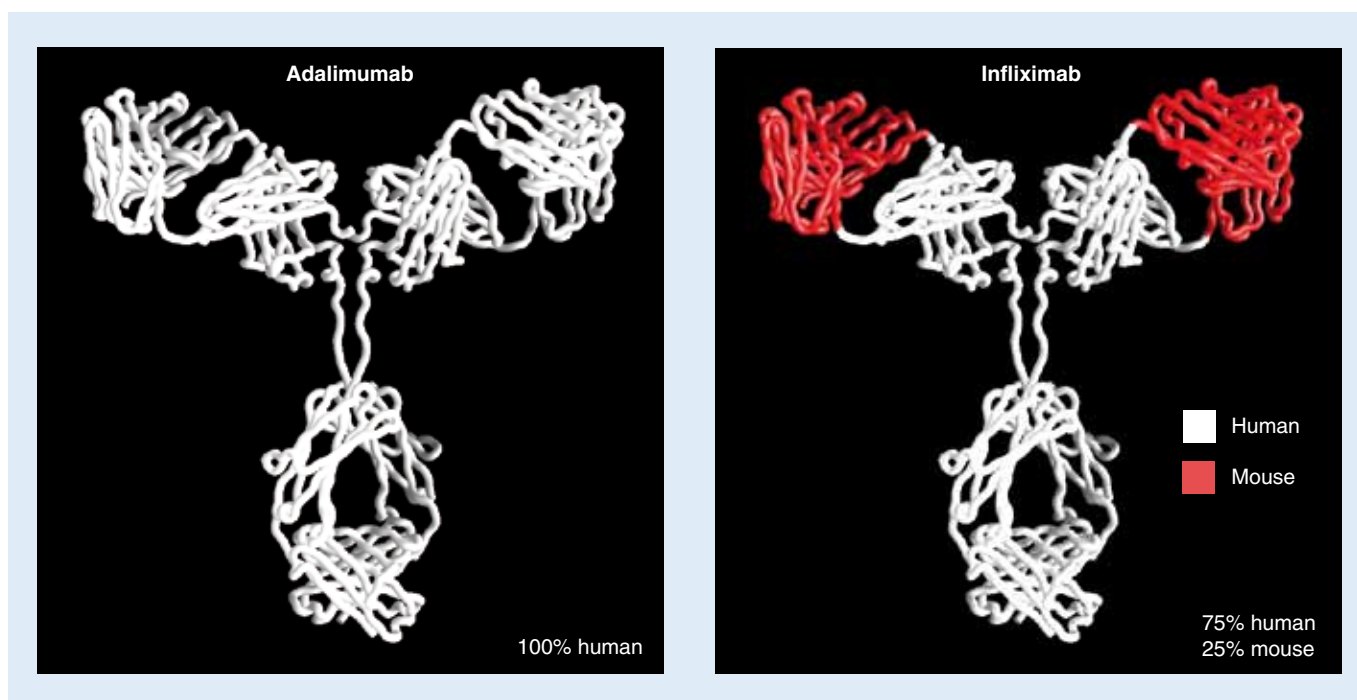


Figure 1. Structure of adalimumab and infliximab. Adalimumab is a anti-TNF- α monoclonal antibody developed through the phage-display library technique with a 100% human peptide sequence. By contrast, infliximab is a chimeric anti-TNF- α monoclonal antibody that contains a 25% murine component.

(FIGURE 1) [8,16]. It is analogous to naturally occurring human IgG1 both structurally and functionally, having a half-life comparable to that of human IgG1 (~14 days). Adalimumab exerts its therapeutic actions by blocking the interaction of TNF- α with the p55 and p75 TNF cell surface receptors.

Chemistry

The molecular weight of adalimumab is approximately 148 kDa, with a chemical formula of $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$.

Pharmacodynamics

Adalimumab exerts its therapeutic actions by blocking the interaction of TNF- α with the p55 and p75 TNF cell surface receptors. Furthermore, adalimumab can lyse TNF- α -expressing cells *in vitro* with or without complement.

Pharmacokinetics

The pharmacokinetic properties of adalimumab are linear. Mean serum adalimumab clearance ranges from 0.012 to 0.017 l/h (0.191–0.290 ml/min) [13]. Furthermore, adalimumab has no significant effect on the pharmacokinetics of MTX, indicating that dose adjustment of MTX is not necessary [17].

Clinical efficacy

Phase I trial

A single-dose, placebo-controlled study of adalimumab was conducted in patients with longstanding active RA [17]. A total of 120 patients participated (adalimumab 89 and placebo 31), and ascending doses (0.5–10 mg/kg) of adalimumab or

placebo were administered intravenously. Single injections of adalimumab showed a rapid onset of clinical effect (24 h to 1 week), with peak efficacy at 1–2 weeks that was sustained for at least 4 weeks. There were no dose-related increases in adverse events.

Phase II trial

A total of 284 RA patients with active and longstanding disease were randomly assigned to different dose groups (0, 20, 40 and 80 mg) and received a subcutaneous weekly injection of test drugs [18]. At 12 weeks, 51% of the 20-mg group, 57% of the 40-mg group, 54% of the 80-mg group and 10% of the placebo group achieved a 20% American College of Rheumatology Response (ACR20), respectively. The 40- and 80-mg doses provided similar benefit. All doses of adalimumab were well tolerated.

Phase III trials

Monotherapy of adalimumab

Monotherapy of adalimumab in RA patients for whom previous DMARD treatment had failed achieved significant, rapid and sustained improvement in disease activity and physical function in a 26-week, double-blind, placebo-controlled trial in which 544 patients were randomized to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly or placebo [19]. ACR20 responses were 35.8, 39.3, 46.0, 53.4 and 19.1%, respectively. Injection-site reactions occurred in 10.6% of adalimumab-treated patients and 0.9% of placebo-treated patients. A multicenter, double-blind study employing subcutaneous injections of 20, 40 and 80 mg and

placebo in 352 Japanese RA patients (the Clinical Investigation in Highly Disease-Affected Rheumatoid Arthritis Patients in Japan with Adalimumab Applying Standard and General Evaluation [CHANGE] study) showed comparable results in efficacy, safety and pharmacokinetics [20]. From these studies, adalimumab 40 mg every other week is speculated to be the appropriate dosage to treat RA patients when used alone.

Combination therapy of adalimumab with MTX

In a 24-week, randomized, double-blind, placebo-controlled study (the Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Patients with Rheumatoid Arthritis), 271 patients with active RA despite treatment with MTX were studied [21]. They were injected subcutaneously with four different doses of adalimumab (0, 20, 40 and 80 mg) every other week in conjunction with concomitant use of MTX. An ACR20 response at week 24 was achieved by a significantly greater proportion of patients in the 20-, 40- and 80-mg adalimumab plus MTX groups (47.8, 67.2 and 65.8, respectively) than in the placebo plus MTX group (14.5%) (FIGURE 2). Onset of response was noted after 1 week of treatment. Adverse effects were observed equally in adalimumab-treated patients and placebo-treated patients. This study was extended for a further 4 years in an open-label

extension study [22]. Of the 271 patients initially enrolled in the study, 262 receiving adalimumab were evaluated. Among these 262 patients, 162 (62%) remained in the study. The reasons for withdrawals were lack of efficacy (8%), adverse events (12%) and other reasons (18%). In 147 patients who completed 4 years of treatment, 43% achieved clinical remission (disease activity score [DAS] < 2.6) and 22% had no physical function abnormalities (health assessment questionnaire [HAQ]: 0). Doses of corticosteroids and MTX could be tapered successfully during the study. There was no difference in serious adverse events between the initial controlled phase and the open-label extension phase.

Adalimumab was shown to inhibit the progression of structural joint damage in active RA patients receiving concomitant MTX in a randomized, placebo-controlled, 52-week trial [23]. In this study, 619 patients with active RA showing inadequate response to MTX were randomized to receive adalimumab 40 mg subcutaneously every other week, adalimumab 20 mg subcutaneously every week or placebo with concomitant MTX. At week 52, there was statistically significantly less radiographic progression, as measured by the change in total Sharp score, in the patients receiving adalimumab either 40 mg every other week (mean $\pm$ standard deviation change: 0.1 ± 4.8) or 20 mg weekly (0.8 ± 4.9) compared with the placebo group (2.7 ± 6.8) (FIGURE 3). Physical

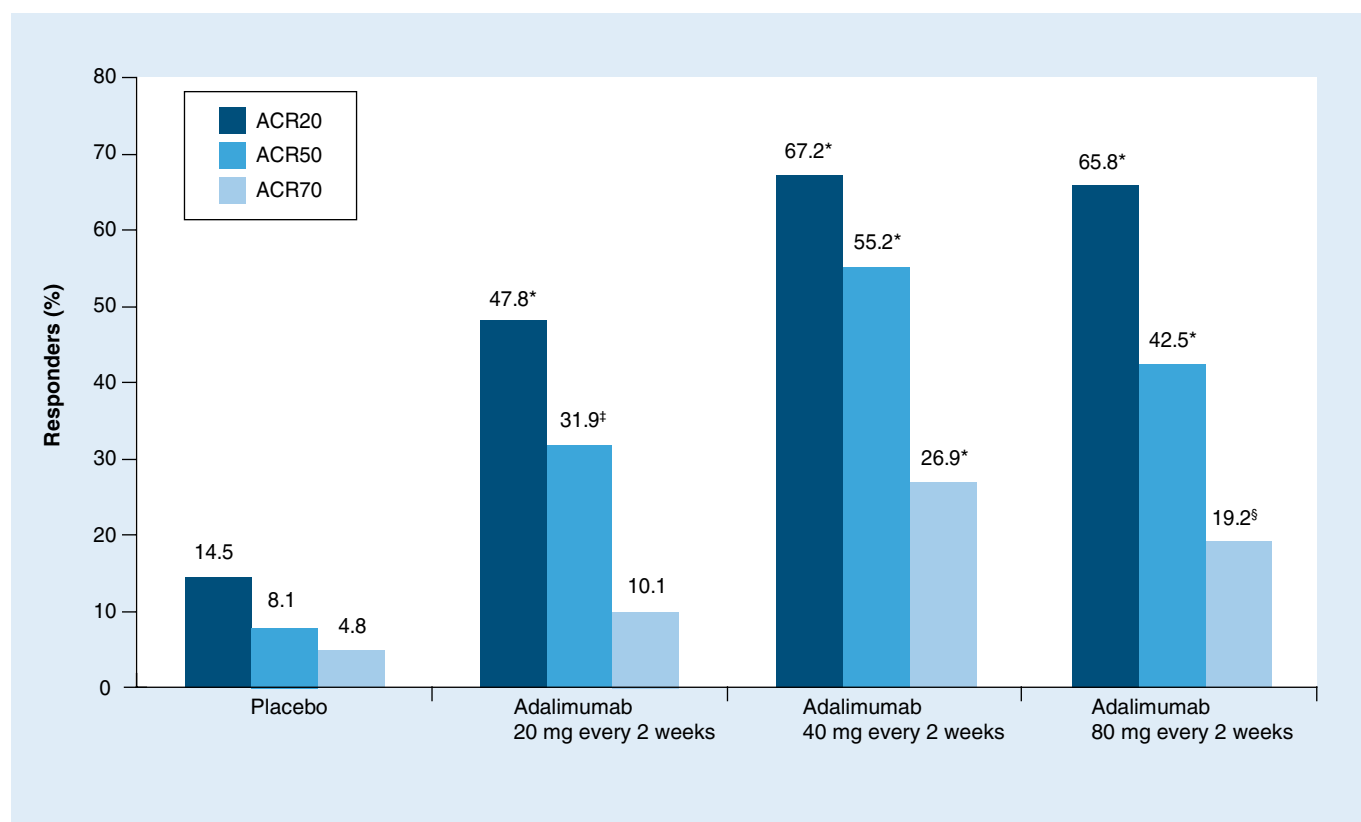


Figure 2. Percentage of rheumatoid arthritis patients who met the ACR criteria for 20, 50 and 70% improvement (ACR20, ACR50 and ACR70, respectively) at week 24.

* $p < 0.001$ versus placebo.

* $p = 0.003$ versus placebo.

[§]0.0020 versus placebo.

ACR: American College of Rheumatology.

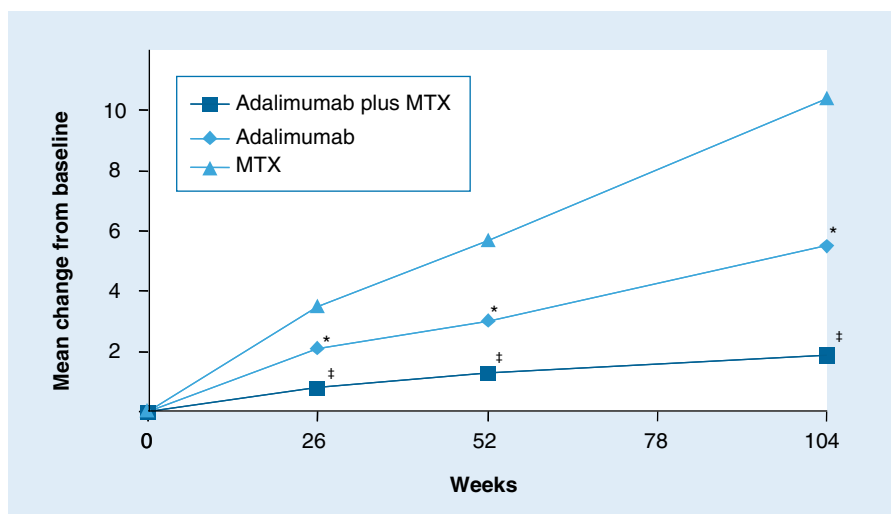


Figure 3. Mean change from baseline in total Sharp scores over time, by treatment group.

* $p < 0.001$ for adalimumab plus MTX versus MTX alone and adalimumab alone.

† $p < 0.001$ for adalimumab versus MTX alone.

MTX: Methotrexate.

function, as measured by the HAQ, demonstrated statistically significant improvement in all adalimumab-treated groups compared with placebo. Adalimumab was generally well tolerated, although the proportion of patients having serious infections was significantly higher in patients receiving adalimumab (3.8%) than in those receiving placebo (0.5%).

In the PREMIER study, in which 799 early, aggressive RA patients who had not received MTX treatment previously were assigned randomly to three groups: adalimumab 40 mg subcutaneously every other week plus MTX, adalimumab 40 mg every other week or weekly oral MTX [24]. Mean disease duration of the patients enrolled in this study was less than 1 year. Combination treatment with adalimumab plus MTX was found to be significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms of disease, inhibiting radiographic progression and inducing clinical remission (FIGURES 3 & 4). Following 2 years of treatment, clinical remission (DAS < 2.6) was obtained in 49% of patients receiving combination therapy, compared with 25% of patients receiving adalimumab alone and 25% of patients taking MTX alone (FIGURE 4). Subanalysis of the PREMIER study compared the Medical Outcome Study Short-Form 36 Health Survey (SF-36) score between RA patients and a normal population in the USA [25]. After 2 years, the quality of life for patients treated with combination therapy improved to a normal level. This study indicates that early intervention with adalimumab plus MTX offers the best opportunity to prevent irreversible joint damage and improve quality of life.

Phase IV trials

Adalimumab 40 mg injected every other week was effective and well tolerated in the Research in Active Rheumatoid Arthritis (ReAct) trial [26]. A total of 20% of 6610 patients achieved clinical remission (DAS < 2.6). Predictors for remission were male

sex, younger age, concomitant DMARD use, lower baseline DAS28, C-reactive protein, HAQ disease index score, comorbidity of less than one and TNF- α antagonist naivety. Of the 6610 patients, 899 had a history of etanercept and/or infliximab therapy, and these patients experienced substantial clinical benefit from adalimumab treatment [27]. At week 12, ACR20 and ACR50 responses were 60 and 33%, respectively (FIGURE 4). Similar findings have been reported from different cohorts of patients [28,29]. In this respect, treatment response to a second or third TNF antagonist has been studied in different cohorts [30,31]. Lack of efficacy was the most common reason for discontinuation, but switching to a second or third biologic is generally effective and well tolerated. Adalimumab was effective and well tolerated in patients with RA who failed infliximab therapy previously, irrespective

of the reason for discontinuation and irrespective of human anti-chimeric antibody against infliximab status [32]. Adalimumab is, therefore, an effective treatment refractory to or intolerant to other TNF- α antagonists. Switching from infliximab to adalimumab was tested in an open-label study, since infliximab is hospital-administered, whereas adalimumab can be self-administered [33]. A switch from infliximab to adalimumab in patients with RA who have responded to infliximab was feasible and well tolerated, with the potential for direct and indirect economic advantages in this cohort.

The effectiveness and medication costs of three TNF- α antagonists (adalimumab, etanercept and infliximab) were compared in the Dutch registry system [34]. The DAS and SF-36 physical component scale decreased in all three groups over 12 months, but the decrease was significantly larger for the adalimumab and etanercept groups than for infliximab groups. The discontinuation rates after 12 months were 22, 21 and 31%, respectively, indicating that the survival rate of infliximab was significantly inferior to both adalimumab and etanercept. HAQ was also better for adalimumab and etanercept than infliximab at 12 months. Furthermore, the total medication costs in the first year for infliximab were significantly higher than those for adalimumab and etanercept.

Safety & tolerability

Adalimumab was well tolerated and serious adverse effects were uncommon in clinical trials [19–24]. Combined treatment with adalimumab and MTX does not alter the incidence and severity of adverse effects [21–24]. However, caution should be advised since some adverse effects, such as infections, have been reported in postmarketing surveillance. The Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR) study, enrolling 636 patients, evaluated the safety of adalimumab 40 mg every other day when

administered with standard antirheumatic therapy in active RA patients not adequately responding to such therapies [35]. At 24 weeks, there were no statistically significant differences between the adalimumab and placebo groups in their respective rates of adverse events (86.5 vs 82.7%), serious adverse events (5.3 vs 6.9%), severe or life-threatening adverse events (11.9 vs 15.4%) or those leading to withdrawal (2.8 vs 2.2%). There were also no statistically significant differences in the rates of infections (52.2 vs 49.4%) or serious infections (1.3 vs 1.9%) between the groups. Another safety analysis of adalimumab in global clinical trials and US postmarketing surveillance of RA patients that covered 10,050 patients representing 12,506 patient-years (PYs) of adalimumab exposure was performed [36]. The rate of serious infections was 5.1 out of 100 PYs, which was comparable to published reports of RA populations naive to anti-TNF- α treatment. The rate of tuberculosis was 0.27 out of 100 PYs. The rate of tuberculosis decreased after implementation of screening and prophylaxis for tuberculosis. The standard incidence ratio (SIR) for lymphoma of 3.19 (95% confidence interval [CI]: 1.78–5.26) was consistent with that of the general RA population. The ReAct trial, representing 4210 PYs of adalimumab exposure, showed that the SIR for malignancy was 0.71 (95% CI: 0.49–1.01) and the SIR for lymphoma was 1.09 (95% CI: 0.12–3.95) [37]. The standardized mortality ratio was 1.07 (95% CI: 0.75–1.49). Development of congestive heart failure, systemic lupus erythematosus and demyelinating disease was also not significant in the adalimumab-treated group. These data demonstrate that long-term adalimumab treatment is generally safe and well tolerated in patients with RA.

The immunogenicity of adalimumab must be mentioned. It has been noted that a substantial proportion of RA patients show little response to, or lose initial response to, adalimumab. Adalimumab is thought to be less immunogenic than chimeric antibodies, but 12% of adalimumab-treated patients were positive for antibodies against adalimumab (AAA) when administered as monotherapy [19]. Among all adalimumab treatment groups combined, the ACR20 response rate at week 26 was lower for patients who were positive for AAA than for those who were negative. However, no significant differences were found between adalimumab- and placebo-treated patients for serious adverse events, serious infections or malignancies. Higher incidences of AAA (37.0%) were found in the CHANGE study with monotherapy of adalimumab performed in Japan, a finding that might be ascribed to racial differences [20]. Further study suggested that these antibodies are anti-idiotypic antibodies. A recent study evaluated the incidence of AAA formation and the association with serum adalimumab concentrations and clinical response assessed by the European League Against Rheumatism (EULAR) criteria [38]. AAA was detected in 17% of the patients during 28 weeks of treatment. EULAR nonresponders had AAA significantly more often than good responders (34 vs 5%). Patients with AAA showed less improvement in disease activity than those without AAA. In addition, high AAA concentrations were associated with the absence of detectable serum adalimumab. Concomitant use of MTX was lower in the group with AAA (52%) than in the group without AAA (84%), suggesting that MTX might suppress AAA formation.

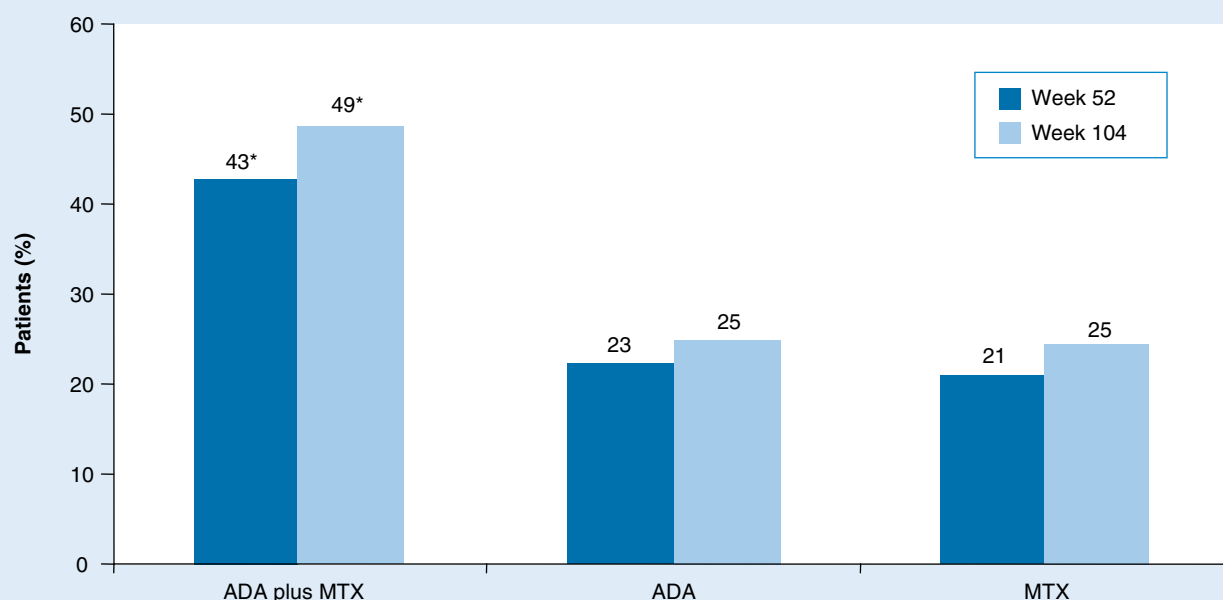


Figure 4. Clinical remission (disease activity score < 2.6) at week 52 and week 104 by treatment group.

* $p < 0.001$ versus ADA alone and versus MTX alone.

ADA: Adalimumab; MTX: Methotrexate.

Vaccinations

Patients on TNF- α antagonists should avoid receiving live vaccines. When live vaccines are required, they should be administered 4 weeks prior to starting treatment [39]. Antibody responses to both influenza and pneumococcal vaccination were not impaired in patients receiving adalimumab.

Pregnancy

There are no detailed clinical studies of adalimumab in pregnancy or lactation. TNF- α antagonists are classified into class B of pregnancy risk.

Regulatory affairs

On the basis of these results, adalimumab was approved as a treatment for RA by the US FDA in the USA in December 2002 and by the EMEA in September 2003. Indications for RA are reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Adalimumab is also indicated as first-line treatment for early RA. It can be used alone or in combination with MTX. Adalimumab has been prescribed to more than 270,000 patients worldwide, including the USA and 74 other countries. Adalimumab in the treatment of psoriatic arthritis has also obtained approval from the FDA and the EMEA in 2005. Adalimumab is also approved for ankylosing spondylitis and Crohn's disease in both the USA and Europe, and recently for moderate-to-severe chronic plaque psoriasis in the USA.

Expert commentary

Adalimumab is significantly effective in treating RA patients resistant to conventional treatment. Improvements of signs and symptoms of RA by adalimumab is rapid and sustained over the long term. Furthermore, it can significantly prevent progression of joint damage and improve quality of life. Although adalimumab can be used alone in patients showing intolerance to MTX, its efficacy is better when used concomitantly with MTX. Combination treatment with adalimumab and MTX against early and aggressive RA in patients induced remission in 49% in the PREMIER study, again supporting the notion of a window of opportunity [24]. The window of opportunity for adalimumab, however, remains to be clarified.

Adalimumab is administered subcutaneously every other week, and self-injection is possible once the patient learns proper handling and storage of medication. Frequent injection, as with etanercept, is not necessary. Biologics that need intravenous injection, such as infliximab and tocilizumab, are inconvenient for patients who travel frequently or those who have difficulty in taking leave. Intravenous infusion is generally more liable to induce serious infusion reactions, whereas subcutaneously injectable drugs, such as adalimumab and etanercept, generally cause injection-site reactions. Adalimumab is less immunogenic than infliximab, although anti-adalimumab antibodies can be produced, especially if it is used alone. It

can be beneficial when infliximab and etanercept have failed [27–29]. Serious adverse effects of adalimumab are infrequent but physicians should be careful in determining the eligibility of patients and should consider the potential risks and benefits of adalimumab therapy. Close monitoring of adverse effects, including infections, is mandatory.

Five-year view

Adalimumab can be used alone or concomitantly with MTX, and can not only ameliorate the signs and symptoms of the disease but can also inhibit the progression of joint destruction and improve quality of life with a superior safety. Adalimumab is even effective in patients with RA treated previously with other biologics. However, at present, it is difficult to predict the efficacy of adalimumab prior to treatment. Genetic polymorphisms may contribute to clinical response, and such studies to identify responders to adalimumab are underway [40]. Furthermore, some patients are refractory to anti-TNF- α therapy. Other problems of adalimumab in RA include its long-term safety and cost-effectiveness. Long-term safety will be verified in pharmacovigilance activities conducted in various registries.

Both golimumab and certolizumab target TNF- α and are currently in clinical trials globally, as described previously [14,15]. Abatacept is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7. It is currently approved for use in RA patients who have had an inadequate response to one or more DMARDs, including TNF- α antagonists [41, 42]. Rituximab, an anti-CD20 monoclonal antibody, is also effective in treating patients refractory to anti-TNF treatment [43]. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, and ofatumumab, a fully human anti-CD20 monoclonal antibody, both target mature B cells [44]. The anti-IL-6 receptor tocilizumab is significantly effective in inhibiting radiographic progression without MTX [45]. Denosumab is designed to target RANK ligand, a protein that acts as the primary signal to activate osteoclasts [46]. Small molecules that can modify cytokine production and signal transduction may be developed to improve the efficacy of the drugs and to reduce medical costs. CP-690,550 is a small-molecule inhibitor of Janus kinase 3, a critical enzyme in the signaling pathway of multiple cytokines (IL-2, -7, -15 and -21) and is being studied in clinical trials for the treatment of RA [47].

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Key issues

- Rheumatoid arthritis (RA) is characterized by the inflammation and destruction of multiple joints, which, in turn, hampers quality of life and shortens the life expectancy of the affected patients.
- The ultimate goals for the treatment of RA are to prevent joint damage and restore normal life.
- Adalimumab is the first anti-TNF- α monoclonal antibody with a 100% human peptide sequence.
- Adalimumab can be used alone or concomitantly with methotrexate, but the combination of both is significantly superior to adalimumab alone.
- Adalimumab can not only ameliorate the signs and symptoms of the disease, but can also inhibit the progression of joint destruction and improve quality of life.
- Adalimumab is even effective in patients with RA treated previously with other biologics.
- Long-term treatment with adalimumab is safe and well tolerated in patients with RA.

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Affiliation

- Nobuyuki Miyasaka, MD
Professor of Medicine and Rheumatology,
Graduate School, Tokyo Medical and
Dental University, 1-5-45, Yushima,
Bunkyo-ku, Tokyo, Japan
Tel.: +81 358 035 201
Fax: +81 356 840 057
miya.rheu@tmd.ac.jp

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