Assessment of long-term safety and efficacy of etanercept in a 5-year extension study in patients with rheumatoid arthritis

L. Klareskog[1], M. Gaubitz[2], V. Rodríguez-Valverde[3], M. Malaise[4], M. Dougados[5], and J. Wajdula[6], for The Etanercept Study 301 Investigators

[1]Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [2]Kooperatives Rheumazentrum Münster, Münster, Germany; [3]Hospital Universitario Marqués de Valdecilla, Facultad de Medicina, Universidad de Cantabria, Santander, Spain; [4]CHU Sart Tilman, Liege, Belgium; [5]Hospital Cochin, Paris, France; [6]Pfizer Inc., Collegeville, Pennsylvania, USA.

Abstract

Objective

To evaluate long-term safety and efficacy of etanercept (ETN) in patients with rheumatoid arthritis (RA) without concomitant disease-modifying antirheumatic drug therapy.

Methods

A total of 549 patients enrolled in this 5-year, open-label extension after completing 1 of 2 randomised controlled studies; all patients received ETN 25 mg twice weekly during the extension. Safety assessments included physical exams, adverse events (AEs), vital signs, laboratory tests, and autoantibody evaluations. Key efficacy endpoints included numbers of responders achieving the American College of Rheumatology (ACR) criteria, low disease activity scores, and disease remission.

Results

Three hundred and eight (56%) patients completed the 5-year extension study. Total ETN exposure, including that received during the double-blind studies was 2212 patient-years. Withdrawals for efficacy- and safety-related reasons were 12% and 19%, respectively. The most common AE was upper respiratory infection (44%). Rates of serious infections decreased over the 5-year period; one case of suspected tuberculosis was reported. Rates of malignancies remained generally consistent during the 5-year period. There were no reports of demyelinating disease, serious blood dyscrasias, or opportunistic infections. The relationship between autoantibody titres and clinical events was not statistically significant. Less than 5% of patients tested positive for anti-etanercept antibodies and all antibodies were non-neutralising. After 5 years, ACR 20, 50, and 70 response rates were 78%, 51%, and 32%, respectively; the mean percentage of patients achieving low disease activity score (DAS ≤2.4) and remission (DAS ≤1.6) were 44% and 20%, respectively.

Conclusion

ETN maintained a favourable safety profile and consistent efficacy throughout the 5-year study duration.

Key words

rheumatoid arthritis, TNF receptor, etanercept, autoantibodies

Lars Klareskog, MD
Markus Gaubitz, MD, PhD
Vicente Rodríguez-Valverde, MD
Michel Malaise, MD
Maxime Dougados, MD
Joseph Wajdula, PhD

Please address correspondence and reprint requests to:
Dr Joseph Wajdula, Assist. Vice President, Worldwide Biopharmaceuticals, Specialty Care, Pfizer Inc., 500 Arcola Road, Collegeville, PA 19426, USA.
E-mail: joseph.wajdula@pfizer.com

Received on May 27, 2010; accepted in revised form on December 15, 2010.

Competing interests: Prof Klareskog has received grants for registry studies in Sweden, and consulted (free of charge) for Pfizer, BMS, AstraZeneca, Abbott, Roche, SP/Merck, and NovoNordisk;
Prof Gaubitz has been a consultant and speaker on symposia arranged by Chugai, Abbott, Essex, Bristol Myers Squibb, Roche and Wyeth;
Prof Dougados has received honoraria from BMS for his participation at symposia or advisory boards organised by BMS and Pfizer Inc.;
Dr Wajdula is an employee of Pfizer Inc., and was an employee of Wyeth, which was acquired by Pfizer Inc. in October 2009;
Profs Malaise and Rodríguez-Valverde have no competing interests.

Introduction

Anti-tumour necrosis factor (anti-TNF-α) therapies are highly effective and generally well tolerated in the treatment of rheumatoid arthritis (RA) (1-9). Of the TNF-α agents currently in use, the relative amount of long-term data with these agents varies and there may be differences in the risk benefit profile.

Etanercept (ETN), a fully human, TNF-α receptor fusion protein, has been shown to reduce disease activity and the progression of joint damage, and had a favourable safety profile in several randomised controlled studies of 6 to 36 months duration (3, 4, 6, 10-13) in patients with RA. When administered in combination with methotrexate, ETN has been shown to halt joint damage within 1 year of treatment (3, 12). This effect on disease progression was maintained throughout the 3-year duration of the study with no unexpected safety events (3).

Changes in immunosurveillance, namely the incidence of infection including serious and opportunistic infections, malignancy, mortality and immunogenicity are concerns associated with RA and anti-TNF-α therapy. This 5-year open-label extension study provides additional data on the long-term efficacy and safety of ETN with a focus on the influence of ETN on immunosurveillance.

Methods

Study design and patients

This open-label, multicentre study was conducted at 58 sites in 12 European countries (see *Appendix*). The study enrolled patients who had previously completed either of 2 randomised, double-blind, placebo-controlled studies (Fig. 1). All patients received ETN 25 mg subcutaneously twice weekly without any concomitant disease-modifying anti-rheumatic drugs (DMARDs). The study design has been published previously (14).

The ethics committee for each participating centre approved the study protocol and the consent form. Before entering the open-label study, each patient gave written informed consent.

Clinical and laboratory evaluation

Safety evaluations included physical examination, reports of adverse events (AEs), vital signs, routine blood biochemistry, and haematology analysis. An AE was considered to be a treatment-emergent adverse event (TEAE) if it occurred during the study or if the severity of a pre-existing event increased during the study. A serious adverse event (SAE) was any event that resulted in death; was life threatening, required hospitalisation, or medical or surgical intervention; resulted in persistent or significant disability, cancer; or a congenital defect. Infections were serious if they met the definition of an SAE.

Evaluation for the presence of anti-ETN antibodies was performed using an enzyme-linked immunosorbent assay (ELISA). Samples positive (2X baseline optical density [OD]) for anti-ETN antibodies were then tested for neutralising activity using competitive ELISA.

Efficacy evaluations included swollen and tender joint counts (66/68 counts), patient's assessment of pain, patient and physician global assessments of disease activity, Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR) levels, and C-reactive protein (CRP) levels.

Statistical analyses

In this open-label study, the emphasis was on descriptive statistics because only 1 treatment group was evaluated. The primary analysis was assessment of long-term safety parameters. The baseline used for safety parameters was the start of the open-label study. Assessment of clinical efficacy of ETN was secondary to the safety endpoint. The main efficacy endpoints were the number of painful and swollen joints. Efficacy parameters were analysed using the last observation carried forward (LOCF) approach and included patients who received at least 1 dose of ETN, the modified intent-to-treat (mITT) population. For efficacy parameters, the baseline values were assessed before the start of ETN treatment. For patients who received ETN, it meant the assessments performed at the baseline visit before the start of the double-blind trials; for patients who received placebo during the double-blind trials,

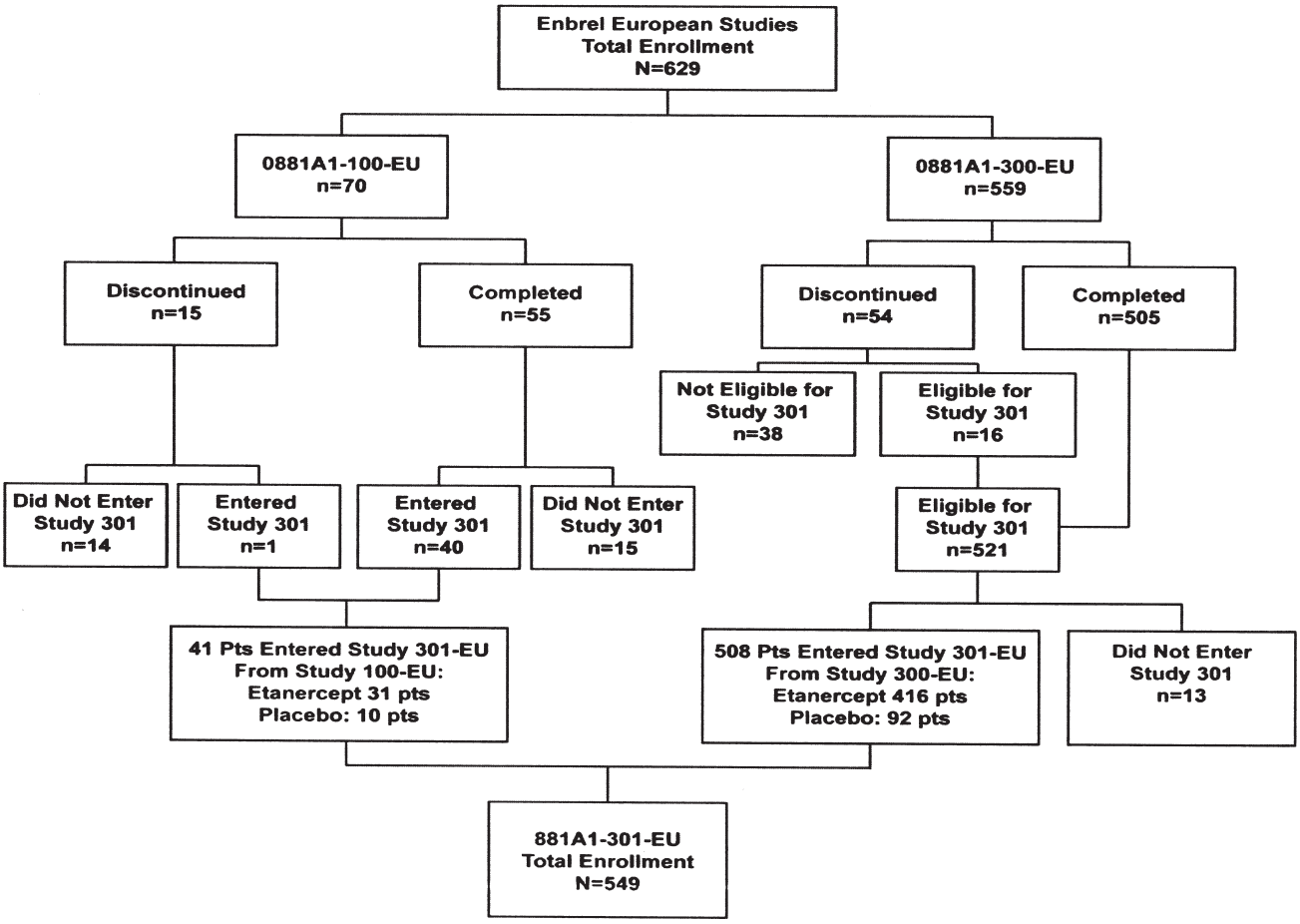

Fig. 1. Flow chart of patients from the double-blind studies to the long-term open-label study.
Study 0881A1-301-EU included patients who had previously completed either study 0881A1-100-EU or study 0881A1-300-EU. Study 0881A1-100-EU was a pharmacokinetic/pharmacodynamic double-blind, placebo-controlled study of etanercept in patients with rheumatoid arthritis. Study 0881A1-300-EU was a double-blind, placebo-controlled study of the efficacy and safety of 4 different doses of etanercept in patients with rheumatoid arthritis.

it was the assessments performed at the last visit before the open-label study.

Malignancy rates were compared to the Surveillance, Epidemiology, and End Results (SEER) database in order to evaluate the expected number of malignant events (15) compared to those reported during the study.

The annual rate of death was compared to the incidence rates for the general US population, adjusted for age and sex (16).

A standardised incidence ratio (SIR) analysis of opportunistic infections, including fungal, protozoal, bacterial, and atypical mycobacterial, was performed. Organisms were selected based upon the Centres' for Disease Control and Prevention (CDC) definition of opportunistic infections, as listed for reference in evaluation of subjects with human immunodeficiency virus (17).

With 549 patients, there was a >90% probability of observing an AE with a true incidence of 1% or more and a 50% probability of observing at least 1 event with a true underlying incidence of 0.13%.

Results

A total of 549 patients, who had previously completed 1 of 2 randomised double-blind studies, were enrolled in this open-label extension (Fig. 1). Baseline demographics, disease characteristics, and RA therapy at entry into the double-blind studies have been published (14).

ETN exposure accrued was 2040 patient-years over the 5 years of the open-label extension and 2212 patient-years when the exposure included the patients receiving ETN during the double-blind studies (Study 100 and 300). The retention rate was 56% after 5 years (Table I).

All discontinuations and the subsets of discontinuations due to adverse events and unsatisfactory response have been charted in a Kaplan-Meier plot (Fig. 2). Although AEs were the most common reason for premature withdrawal from the study (Table I), there was no clustering of AEs that were predominantly responsible for patient withdrawals. After year 3, the cumulative discontinuation rate because of unsatisfactory response remained essentially constant until the end of the study.

Safety

The most frequently reported TEAEs were upper respiratory infection, accidental injury, injection site reaction, flu syndrome, and infection (Table II). There were no cases of demyelinating disease of the central nervous system or blood dyscrasias.

Of a total of 302 SAEs reported during the study, 106 resulted in discontinuations and 16 resulted in deaths. Yearly

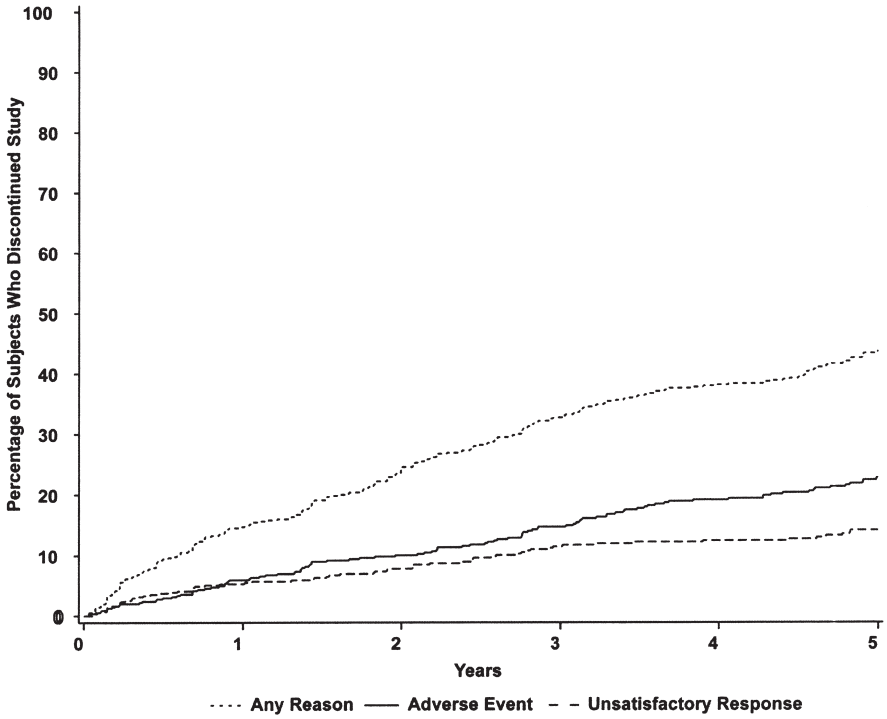

Fig. 2. Kaplan-Meier plot of discontinuations over the 5-year duration of the study.

rates of serious infections, deaths, and malignancies are presented in Table III. A total of 94 patients reported 130 serious infections during the study; the most commonly reported serious infections according to COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) preferred terms were infection (n=18; 0.882 per 100 patient-years), pneumonia (n=15; 0.735 per 100 patient-years), sepsis (n=15; 0.735 per 100 patient-years), abscess (n=11; 0.539 per 100 patient-years), bronchitis (n=8; 0.392 per 100 patient-years), and pyogenic arthritis (n=8; 0.392 per 100 patient-years).

Of the 14 patients with a history of tuberculosis (TB), none experienced TB reactivation. One case of suspected TB was reported in a patient from Spain with a history of occupational pneumoconiosis (Caplan syndrome). This patient had a positive tuberculin test without evidence of mycobacterium and

Table I. Primary reason for study withdrawal*.

Reason	no. (%)
Any reason for withdrawal	241 (44%)
Adverse event	106 (19%)
Unsatisfactory response	67 (12%)
Other nonmedical event	28 (5%)
Patient request	23 (4%)
Protocol violation	13 (2%)
Failed to return	4 (<1%)

*Values refer to the number (%).

Table II. Treatment-emergent adverse events (≥10%).

TEAE	% of patients
Upper respiratory infection	44
Accidental injury	36
Injection site reaction	28
Flu syndrome	26
Infection	26
Abdominal pain	20
Back pain	20
Pharyngitis	19
Bronchitis	18
Headache	18
Rash	18
Cough increased	17
Rhinitis	17
Arthralgia	16
Diarrhoea	15
Hypertension	15
Urinary tract infection	13
Gastroenteritis	12
Asthenia	11
Injection site hemorrhages	11
Pain	11
Pruritus	11
Depression	10
Nausea	10

Table III. Medically important safety events over 5 years.

Parameter	Years on Etanercept						
	Year 1 (n=549)	Year 2 (n=469)	Year 3 (n=420)	Year 4 (n=369)	Year 5 (n=340)	Year >5 (n=263)	Total (n=549)
Patient-years	496	441	389	347	321	47	2040
Serious infections							
No. of events	37	26	26	21	17	3	130
Infections per 100 patient-years	7.5	5.9	6.7	6.1	5.3	6.4	6.4
Deaths							
No. of events	4	0	3	6	2	1	16
Deaths per 100 patient-years	0.8	0	0.8	1.7	0.6	2.1	0.8
Patient-years*	518.4	455.4	403.6	359.0	333.1	142.8	2212
Malignancies							
No. of events	4	7	3	5	2	1	22†
Malignancies per 100 patient-years	0.772	1.537	0.743	1.393	0.300	1.400	0.995

*Includes double-blind and open-label exposure data for those patients who entered the extension trial. †Includes 4 cases of non-melanoma skin cancers. Expected cases: 18.7 based on the NCI SEER database.

Table IV. Types of malignancies.

Event	No. of event
Acute myeloblastic leukemia	1
Breast carcinoma	5
Bladder carcinoma	1
Disseminated carcinoma	1
Gastrointestinal neoplasia/carcinoma	3
Lung carcinoma	3
Lymphoma	1
Mouth carcinoma	1
Myeloma	1
Ovarian carcinoma	1
Skin carcinoma*	4
Total	22

*3 cases of basal cell carcinoma and 1 case of squamous cell carcinoma (reported 3 months after study completion).

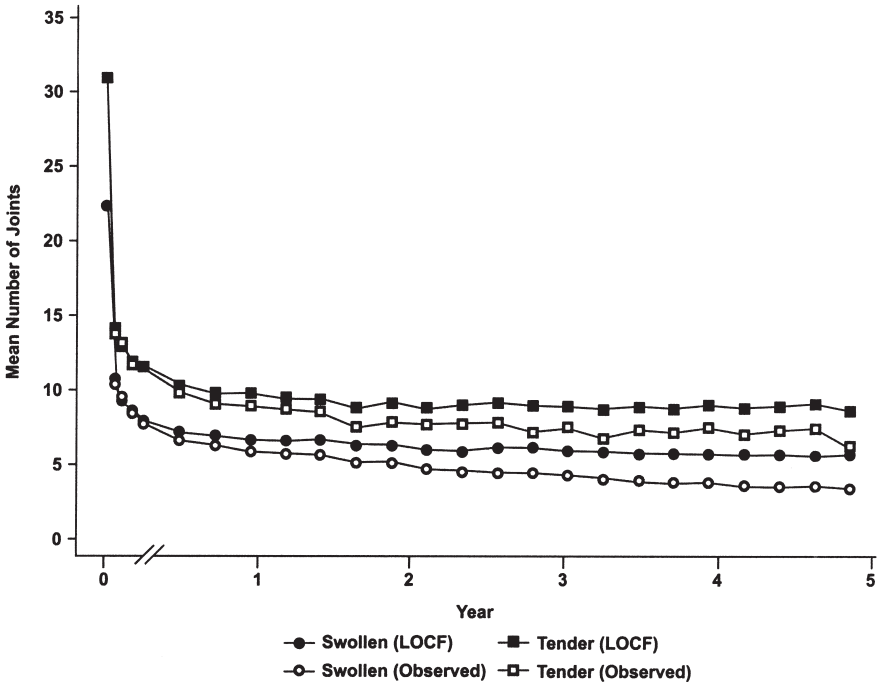

Fig. 3. Mean number of tender/painful joints and swollen joints.
LOCF: last observation carried forward.

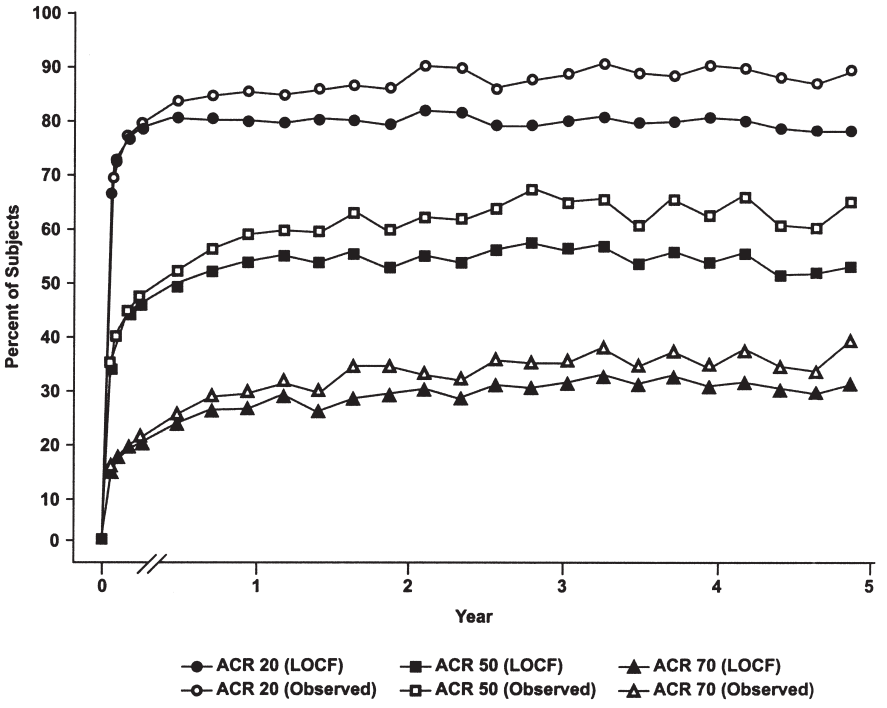

Fig. 4. Percentage of patients achieving ACR 20, ACR 50, and ACR 70 response rates.
ACR: American College of Rheumatology; LOCF: last observation carried forward.

was withdrawn from the study. There were no reports of opportunistic infections caused by atypical mycobacteria, bacteria, fungi, or protozoa.

The number of malignancies observed in this study was compared with the expected rates of cancers in an age- and sex- matched cohort from the US general population, using the National Cancer Institute SEER database (15). The expected number calculated from the SEER database, which excludes non-melanoma skin cancers, was 18.7, which is similar to the 18 cases (excluding 4 non-melanoma skin cancers) observed in this study.

The numbers of cases of malignancies reported yearly remained stable over the course of the study (Table III). The types and numbers of cases reported during the 5 years of this open-label study are shown in Table IV. Other than the 1 previously reported case of lymphoma (14), which occurred during year 1, there were no additional cases of lymphoma reported during the 5 years of the study. This 1 lymphoma reported during the study was similar to the expected number (0.7) for the general US population, calculated from the SEER database (15). The SIR was 1.4 (95% CI: 0.04–8.02) for the number of lymphomas observed *versus* the number expected in the general US population. During this 5-year study, the total number of deaths was 16 (Table III), which is lower than the expected 21 deaths using the incidence rates for the general US population, adjusted for age and sex (16). Five of the deaths reported were the outcomes of AEs involving the cardiovascular system. The number of deaths did not increase with increasing exposure to ETN (Table III).

Over the 5 years, there were no reports of grade 4 laboratory test abnormalities associated with an AE; 7 events of grade 3 laboratory abnormalities were associated with AEs. These events led to 5 patients withdrawing from the study because of the following associated AEs: elevated levels of hepatic transaminases

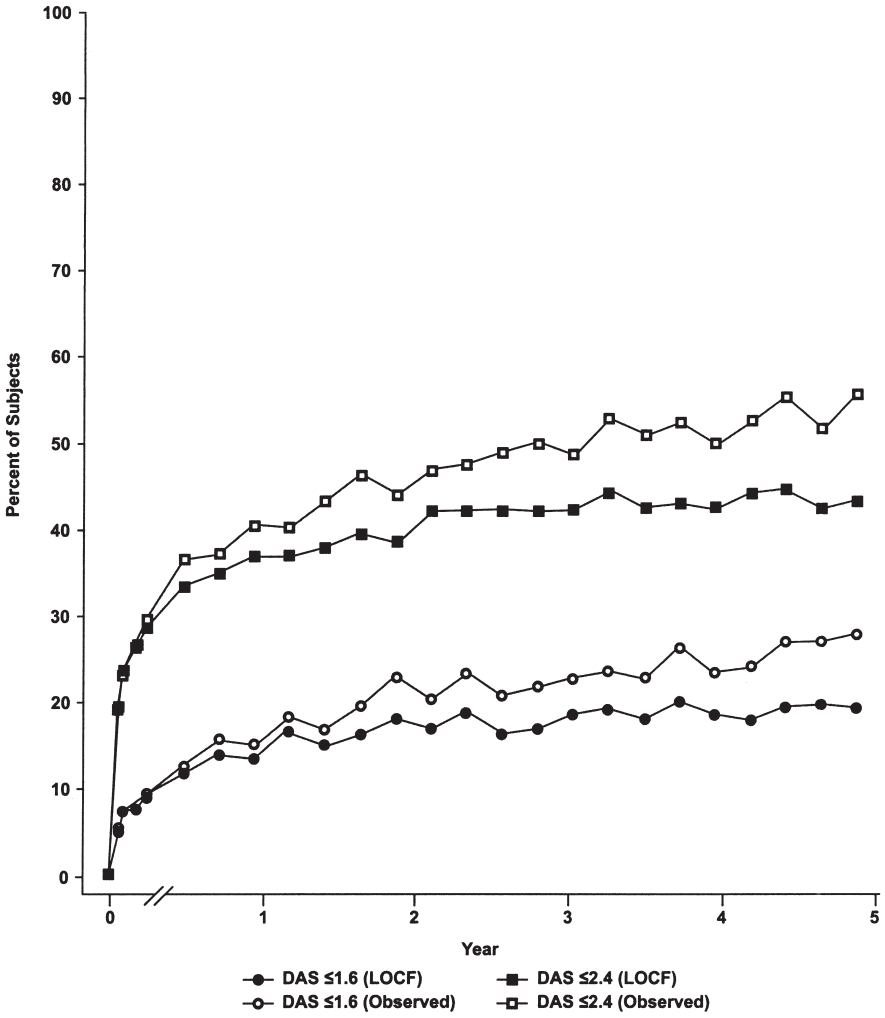

Fig. 5. Percentage (%) of patients achieving DAS ≤2.4 (Low Disease Activity) and DAS ≤1.6 (Remission).
DAS: Disease Activity Score; LOCF: last observation carried forward.

Table V. Mean percentage (%) improvement from baseline for disease activity variables.

Variable	Year				
	1 n=549	2 n=469	3 n=420	4 n=369	5 n=340
Pain (visual analogue scale)	48	49	49	48	49
Physician global assessment	57	60	60	58	58
Patient global assessment	49	49	48	48	48
Health Assessment Questionnaire	41	41	40	39	40
C-reactive protein (mg/L)	26	24	17	26	23
Erythrocyte sedimentation rate	28	28	24	26	23
Disease Activity Score	46	49	49	49	49
Duration of morning stiffness (min)	63	69	73	73	72

(n=2), alcoholic hepatitis (n=1), cholecystitis (n=1), and pyelonephritis (n=1). Many of the reports of grade 3 laboratory abnormalities were isolated events that were normal in subsequent tests.
At each visit up to week 193, ~5% of the patients tested positive for anti-etanercept antibodies and the incidence of patients with 3 or more positive results was 5.4%. Antibodies were transient in nature and all antibodies were non-neutralising. There was no statistically significant difference in the overall incidence of AEs, injection site reactions, allergic reactions, and discontinuations from the study due to AEs between patients who tested positive or negative for anti-etanercept antibodies at 1 or more time points.

Efficacy

The mean number of tender or painful joints and swollen joints decreased dramatically shortly after treatment with ETN and remained consistently low, thereafter (Fig. 3). At 5 years, the numbers were reduced from 31.0 and 22.4, respectively to 8.6 (-72%) and 5.7 (-74%) in the LOCF analysis and to 6.0 (-81%) and 3.5 (-84%) in the observed results.
The percentage of patients meeting ACR 20 criteria increased sharply shortly after ETN was initiated and remained relatively constant thereafter. At 5 years, ACR 20, ACR 50, and ACR 70 scores were achieved by 78%, 51%, and 32% of patients by LOCF analysis and 90%, 61%, and 37% in the observed results (Fig. 4).
At 5 years, the percentage of patients achieving low disease activity measured by disease activity score (DAS) ≤2.4 and disease remission measured by DAS ≤1.6 were 44% and 20%, respectively by LOCF analysis (Fig. 5). In the observed results, the percentage of patients achieving low disease activity and remission were 54% and 30%, respectively.
Significant improvements occurred in several key measures of disease activity, such as patient's assessment of pain, physician's and patient's global assessments, HAQ, CRP, ESR, disease activity score (DAS), and duration of morning stiffness, during the first month of ETN therapy (14). These improvements were sustained through year 5 of the study (Table V).
To determine whether anti-etanercept antibodies result in reduced efficacy, the mean numbers of swollen and painful joints were compared between patients positive for these antibodies versus all patients (Tables VI and VII). The mean number of painful and swollen joints in patients with a positive anti-etanercept antibody test was similar to those without anti-etanercept antibodies.

Table VI. Mean change from baseline of tender joint counts for patients who tested positive for anti-etanercept antibodies (LOCF).

Tender Joint Counts					
	Patients with positive anti-etanercept antibodies			All patients (n=549)	
Visit	no. patients	Baseline mean	Mean change from baseline for patients	Baseline mean	Mean change from baseline
Week 49	33	28.3	20.6	31.0	21.2
Week 97	18	30.6	22.2	31.0	21.9
Week 145	23	36.1	25.5	31.0	22.1
Week 193	8	39.3	24.1	31.0	22.3

LOCF: last observation carried forward.

Table VII. Mean change from baseline of swollen joint counts for patients who tested positive for anti-etanercept antibodies (LOCF).

Swollen Joint Counts					
	Patients with positive anti-etanercept antibodies			All patients (n=549)	
Visit	no. patients	Baseline mean	Mean change from baseline for patients	Baseline mean	Mean change from baseline
Week 49	33	22.2	15.6	22.4	15.8
Week 97	18	18.5	10.4	22.4	16.2
Week 145	23	27.0	20.4	22.4	16.3
Week 193	8	22.9	17.8	22.4	16.7

LOCF: last observation carried forward.

Discussion

The introduction of ETN and other TNF-α inhibitors in the late 1990s has had a substantial impact on treatment paradigms for RA. Because RA is a chronic disease requiring long-term treatment, increasing attention has been paid to the long-term safety profile of these therapies. The theoretical and clinical concerns associated with anti-TNF-α therapy have been focused on changes in immunosurveillance, namely the incidence of infection including serious and opportunistic infections, malignancy, and immunogenicity. In the only other 5-year study evaluating etanercept, a favourable safety profile has been provided for ETN in the treatment patients with ankylosing spondylitis (18). The data collected from RA patients in this open-label experience provides 5 years of additional safety information on the long-term use of ETN and associated risk-benefit profile.

There are a number of reports in the literature regarding the potential for anti-TNF-α therapy to increase serious infections in RA patients due to the important role of TNF-α in host defense (19, 20). It has been shown that patients with RA have an increased risk for serious infections compared to the general population (21, 22). The increase may be due to the immune dysfunction associated with RA, the effects of therapeutic agents, or a combination of these factors (22).

Over the 5-year duration of ETN treatment in this study, the rate of serious infections was 6.4 events/100 patient-years. In the 3-year randomised-controlled TEMPO study (3), the rates of serious infections were 4.6 events/100 patient-years and 5.7 events/100 patient-years for patients receiving ETN and methotrexate, respectively. A retrospectively defined, longitudinal, population-based cohort study of 609 RA patients, who were predominately naïve to anti-TNF-α agents, reported a rate of 9.6 events/100 patient-years for patients primarily treated with conventional DMARDs (23).

In the British Society for Rheumatology Biologics Register (BSRBR) study (24), after adjusting for baseline risk, there was no difference in the overall rate of serious infections reported by patients who received ETN (5.13 events/100 patient-years [95% CI: 4.47-5.85]) compared to those receiving traditional DMARD therapy (4.1 events/100 patient-years [95% CI: 3.14-5.35]). An analysis of serious infections in patients enrolled in the German Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT) Registry found that the rates for etanercept (6.4; 95% CI: 4.5-9.1) and infliximab (6.2; 95% CI: 4.0-9.5) were higher than that reported by patients receiving conventional DMARDs (2.3: 95% CI: 1.3-3.9; p=0.0016) (25). However, it should be noted that more than 50% of patients receiving etanercept and 90% receiving infliximab were also receiving concomitant DMARD therapy. In Swedish patients with RA, Askling *et al*. observed a small increase in the rate of hospitalisations for infections during the first year of therapy with anti-TNF agents compared with anti-TNF-naïve controls (rate ratio [RR] 1.43; 95% CI: 1.18-1.73) (26). The difference diminished over time (0.82; 0.62 to 1.08) for patients remaining on their first anti-TNF treatment for more than 2 years. Based on the reports above, patients treated with ETN in the long-term management of RA appear to have only a limited increased risk for serious infection over patients treated with DMARDS.

Given the known mechanism of action of TNF-α inhibitors, there is interest in determining their potential for increasing the risk of opportunistic infections. It has been noted in the literature that preclinical and clinical data indicate that there is an increased risk of TB (newly acquired and reactivation) and other granulomatous infections associated with anti-TNF-α therapies (24, 27-29). In passive surveillance studies of patients with RA or Crohn's disease and treated with ETN, infliximab (INF), or adalimumab (ADA), differences were observed in the incidence of granulomatous infections including TB, histoplasmosis, listeriosis, and coccidioidomycosis, with ETN having fewer events than INF and ADA (29). Wallis *et al*. (27) observed similar find-

ings while comparing ETN and INF using the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) reports from 1998 through the third quarter of 2002; the overall risk of granulomatous infection was significantly greater ($p<0.001$) in patients treated with INF compared to those treated with ETN. Interestingly, in the current study only 1 case of new onset TB was reported and no reports of opportunistic infections caused by atypical mycobacteria, bacteria, fungi, or protozoa after 5 years of treatment were observed.

While the specific reasons for the lower rate of TB and other granulomatous infections observed in ETN-treated patients remains unclear it may be related to differences in the mechanisms of action. For example, ETN primarily binds soluble TNF and is known to have fast rates of association and dissociation with TNF. The rate of binding specificity suggests that ETN may only transiently neutralise the activity of an individual TNF molecule. In contrast, the binding characteristics of infliximab are consistent with causing a more complete and sustained neutralisation of TNF (30, 31). The differences in TNF binding specificities between ETN and IFN may have differential effects on host defenses (30, 31). Another potential explanation for the seemingly lower incidence of TB with ETN treatment compared to treatment with monoclonal anti-TNF agents may be differences in T-cell activation and IFN-γ production. Saliu *et al*. reported that *in vitro*, INF and ADA inhibit T-cell activation and IFN-γ production, immune responses critical to protection against TB, whereas ETN did not (32).

Due to the importance of TNF-α in tumour surveillance it has been suggested that TNF inhibitors may be associated with an increased risk of malignancy (33, 35). Thus, long-term follow-up in clinical trials is critical in evaluating the risk of developing malignancy with chronic administration of TNF-α therapy. There were 18 SEER cancers and 4 non-melanoma skin cancers over the 5-year follow-up period. The incidence of malignancies was relatively constant for each of the 5 years of treatment with no unusual clustering of any particular cancer. The 18 observed cases of malignancy, not including non-melanoma skin cancers, are similar to the expected 18.7 cases based on the age- and sex-matched general population from the SEER database (15), a database of cancers that have been reported in North America. There was 1 reported case of lymphoma (14), similar to the expected number of lymphoma cases (0.7) from the SEER database. This is also similar to the solid tumour malignancy SIR observed in the Swedish Biologic Register (ARTIS) in which the TNF-α antagonist RA cohort was 0.9 (95% CI: 0.7-1.2) compared to the early arthritis RA cohort (SIR=1.1, 95% CI: 0.9-1.3) (36, 37).

Recently, a meta-analysis was conducted evaluating data from randomised controlled trials of ETN. In this analysis conducted by Bongartz *et al*. (38), 9 ETN RA trials were evaluated for the incidence of treatment-emergent SEER and Non-Melanoma Skin Cancer (NMSC) malignancies. In the combined analysis of SEER and NMSC the difference between the ETN and control groups was not statistically significant (hazard ratio (HR) 1.84 [95% CI: 0.79-4.28]; $p=0.16$). In other analyses from observational studies and registries, patients treated with anti-TNF therapies (39-43), including ETN (39-41, 43), were at no higher risk of malignancy than those not treated with anti-TNF agents. A similar conclusion was drawn from an analysis of combined data from the Swedish Biologics Register, Swedish Registers of RA, and the Swedish Cancer Register (44).

The risk of mortality is generally higher in the RA population compared with the general population (45-48). It has been reported that the lifespan of a patient with inflammatory rheumatic disease, including RA, is 5 to 15 years less than someone of the same sex and age without the disease (46). While the RA population experiences earlier cardiovascular disease and an increase incidence of infection, pulmonary, gastrointestinal, and renal disease, the causes of death are similar to the general population (46, 49). The causes of death in this study were varied; the most common cause of death was due to infection. Of note, the rate of infection did not increase with increased exposure, *i.e*. over the duration of the study.

Over the 5-year course of this study, there were 16 deaths. This was lower than the 21 deaths expected for the general US population (50), adjusted for age and sex over the same period. The lower mortality rate observed in this study correlates with an analysis by Carmona *et al*. (51), which indicated that overall mortality was reduced in RA patients receiving treatment with TNF-α antagonists compared to those who were anti-TNF-α naive (RR 0.32; 95% CI 0.20 to 0.53; $p<0.001$). However, it should be noted that patients who discontinued early were followed up to the time of discontinuation and for 30 days thereafter. This was a limitation to the current analysis because patients who withdrew early from this study were not followed and therefore, their data is not included in the safety results presented. Also, patients recruited to clinical trials, such as the current one, may have a generally lower mortality than an average RA population because the seriously ill patients or patients with serious comorbidities are excluded during the recruitment process.

Previous reports describe a potential correlation between baseline disease severity and risk of death (49, 52). Elevated measures of disease activity, such as ESR, CRP, and the number of tender and swollen joints, may be important predictors of premature death. Thus, reduction and control of disease activity may decrease the risk of early death in patients with RA. This makes the survival rates in this study of particular interest given the severity of baseline disease in the ETN population of this study. Mean ESR and mean CRP, at baseline were 44.3 and 44.4 mg/dL; at 5-years these markers of disease activity were reduced to 31.0, and 22.4 respectively. At 5 years, the mean numbers of tender and swollen joints were reduced from 31.0 at baseline to 8.6 and 22.4 at baseline to 5.7, respectively.

Immunogenicity associated with long-term administration of biologic agents is another area of clinical concern. It

has been shown that administration of biologic preparations can induce the formation of a variety of antibodies. In assessing the clinical impact of these antibodies, it is important to recognise that antibodies produced by the various biologic agents such as human anti-chimeric antibodies (HACA) and human anti-human antibodies (HAHA) have been associated with diminished treatment response (53, 54). In this study ~5% of patients tested positive for anti-etanercept antibodies at 1 or more time points; these antibodies were non-neutralising by assay and did not affect either the efficacy or safety profile of ETN in these patients.

In addition to the immune-mediated effects of biological agents on various safety outcomes, attention to maintenance of long-term efficacy is a key consideration in the management of RA. Overall, after 5 years of exposure there was no attenuation of the therapeutic response.

In conclusion, the safety and efficacy results of this 5-year open-label study in European RA patients are consistent with those reported in previously published double-blind and open-label studies as well as registry data. A favourable risk benefit assessment for ETN was obtained in this cohort of patients as it was well tolerated, no unexpected safety concerns were identified, and there was no loss of efficacy over time.

Acknowledgments

This study was funded by Wyeth Pharmaceuticals, which was acquired by Pfizer Inc., in October 2009. Medical writing support for this article was provided by Ruth Pereira, PhD, Tracey Fletcher, and Stephanie Gaylord at Pfizer Inc., and was funded by Wyeth Pharmaceuticals.

Appendix

Etanercept Study 301 Investigators

A. Alonso Ruiz, Baracaldo, Spain;
D. Andersone, Pilsonu, Latvia;
J.M. Aranburu, Bilbao, Spain;
P.A. Bacon, Birmingham, UK;
P. Benito Ruiz, Barcelona, Spain;
H.J. Bergerhausen, Recklinghausen, Germany;
P. Bertin, Limoges, France;
U. Botzenhardt, Bremen, Germany;
H. Bird, West Yorkshire, UK;
J. Bratt, Huddinge, Sweden;
L. Carreno, Madrid, Spain;
J. Castenhag, Karlstad, Sweden;
G. Chales, Rennes, France;
R. Dahl, Uppsala, Sweden;
B. Danneskiold-Samsoe, Frederiksberg, Denmark;
M. Dougados, Paris, France;
G. Ferraccioli, Udine, Italy;
M. Figueroa, San Sebastian, Spain;
O. Forre, Oslo, Norway;
S. Freiesleben Sorensen, København, Denmark;
M. Gaubitz, Münster, Germany;
J. Gijon, Madrid, Spain;
J.J. Gomez Reino, Santiago De Compostela, Spain;
J. Goobar, Östersund, Sweden;
N. Graudal, Herlev, Denmark;
H. Haentzschel, Leipzig, Germany;
G. Hein, Jena, Germany;
J.R. Kalden, Erlangen, Germany;
J.P. Kaltwasser, Frankfurt, Germany;
J.L. Kuntz, Strasbourg, France;
H. Lang, Plauen, Germany;
I. Leden, Kristianstad, Sweden;
B. Lindell, Kalmar, Sweden;
M. Malaise, Liège, Belgium;
E. Martin Mola, Madrid, Spain;
O. Meyer, Paris, France;
N. Misiuniene, Kaunas, Lithuania;
M. Mousa, Visby, Sweden;
H. Nielsen, Herlev, Denmark;
M. Nissila, Heinola, Finland;
H. Nusslein, Dresden, Germany;
T. Helve, Helsinki, Finland;
O. Karjalainen, Oulu, Finland;
L. Klareskog, Stockholm, Sweden;
M. Korpela, Pikonlinna, Finland;
R. Luukkainen, Rauma, Finland;
J.L. Marenco, Sevilla, Spain;
R. Oding, Vasteras, Sweden;
J.L. Pasquali, Strasborg, France;
E. Rankin, Birmingham, UK;
V. Rodriguez Valverde, Santander, Spain;
J. Sany, Montpellier, France;
L. Sköldstam, Kalmar, Sweden;
G. Simenon, Bruxelles, Belgium;
J.G. Tebib, Pierre Benite, France;
J. Tornero, Guadalajara, Spain;
S. Transo, Jonkoping, Sweden;
M. Vallgarda Ojlert, Orebro, Sweden;
H. Warnatz, Essen, Germany;
D. Wendling, Besancon, France;
A. Wittenborg, Recklinghausen, Germany;
H. Zeidler, Hannover, Germany.

References

1. BRAUN J, KALDEN JR: Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27: S164-7.
2. VAN DER HEIJDE D, KLARESKOG L, RODRÍGUEZ-VALVERDE V *ehyt al*.: Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; 54: 1063-74.
3. VAN DER HEIJDE D, KLARESKOG L, LANDEWÉ R *et al*.: Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 3928-39.
4. BATHON JM, MARTIN RW, FLEISCHMANN RM *et al*.: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586-93.
5. WEINBLATT ME, KEYSTONE EC, FURST DE *et al*.: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
6. WEINBLATT ME, KREMER JM, BANKHURST AD *et al*.: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.
7. MAINI R, ST CLAIR EW, BREEDVELD F *et al*.: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.
8. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
9. 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* 2006; 54: 26-37.
10. MORELAND LW, SCHIFF MH, BAUMGARTNER SW *et al*.: Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Int Med* 1999; 130: 478-86.
11. GENOVESE MC, BATHON JM, MARTIN RW *et al*.: Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46: 1443-50.
12. KLARESKOG L, VAN DER HEIJDE D, DE JAGER JP *et al*.: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis. *Lancet* 2004; 363: 675-81.

13. MORELAND LW, BAUMGARTNER SW, SCHIFF MH *et al*.: Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *New Engl J Med* 1997; 337: 141-7.
14. KLARESKOG L, GAUBITZ M, RODRÍGUEZ-VALVERDE V, MALAISE M, DOUGADOS M, WAJDULA J: A long-term, open-label trial of the safety and efficacy of Etanercept (ENBREL®) in patients with rheumatoid arthritis not treated with other DMARDs (3-year interim report). *Ann Rheum Dis* 2006; 65: 1578-84.
15. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1999 [11 Registries, 1992-1999]) National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2002, based on the November 2001 submission. http://www.seer.cancer.gov.
16. KOCHANEK KD, SMITH BL, ANDERSON RN. Deaths: preliminary data for 1999. *Natl Vital Stat Rep* 2001; 49: 1-48.
17. BENSON CA, KAPLAN JE, MASUR H, PAU A, HOLMES KK: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR Recomm Rep* 2004; 53: 1-112.
18. MARTIN MOLA E, SIEPER J, LEIRISALO-REPO M *et al*.: Sustained efficacy and safety, including patient-reported outcomes, with etanercept treatment over 5 years in patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2010; 28: 238-45.
19. 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* 2006; 295: 2275-85.
20. RIJNEVELD AW, FLORQUIN S, BRANGER J, SPEELMAN P, VAN DEVENTER SJ, VAN DER POLL T: TNF-alpha compensates for the impaired host defense of IL-1 type I receptor-deficient mice during pneumococcal pneumonia. *J Immunol* 2001; 167: 5240-6.
21. DORAN MF, CROWSON CS, POND GR, O'FALLON WM, GABRIEL SE: Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002; 46: 2287-93.
22. SMITTEN AL, CHOI HK, HOCHBERG MC *et al*.: The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol* 2008; 35: 387-93.
23. MORELAND LW, WEINBLATT ME, KEYSTONE EC *et al*.: Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006; 33: 854-61.
24. DIXON WG, WATSON K, LUNT M, HYRICH KL, SILMAN AJ, SYMMONS DP: Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; 54: 2368-76.
25. LISTING J, STRANGFELD A, KARY S *et al*.: Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005; 52: 3403-12.
26. ASKLING J, FORED CM, BRANDT L *et al*.: Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis* 2007; 66: 1339-44.
27. WALLIS RS: Reconsidering adjuvant immunotherapy for tuberculosis. *Clin Infect Dis* 2005; 41: 201-8.
28. FURST DE, WALLIS R, BRODER M, BEENHOUWER DO: Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum* 2006; 36: 159-67.
29. KEYSTONE EC: Safety of biologic therapies--an update. *J Rheumatol Suppl* 2005; 74: 8-12.
30. WALLIS RS: Anti-tuberculosis treatment and infliximab. *Respir Med* 2005; 99: 1620-2.
31. SCALLON B, CAI A, SOLOWSKI N *et al*.: Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002; 301: 418-26.
32. SALIU OY, SOFER C, STEIN DS, SCHWANDER SK, WALLIS RS: Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis* 2006; 194: 486-92.
33. WOLFE F, MICHAUD K: Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; 50: 1740-51.
34. DEVOOGDT N, REVETS H, KINDT A, LIU YQ, DE BAETSELIER P, GHASSABEH GH: The tumor-promoting effect of TNF-alpha involves the induction of secretory leukocyte protease inhibitor. *J Immunol* 2006; 177: 8046-52.
35. DZIADZIO M, SMITH R: Meta-analysis is no substitute for a comprehensive national registry. *Clin Rheumatol* 2007; 26: 1134-5.
36. ASKLING J, FORED CM, BRANDT L *et al*.: Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64: 1421-6.
37. ASKLING J, FORED CM, GEBOREK P *et al*.: Swedish registers to examine drug safety and clinical issues in RA. *Ann Rheum Dis* 2006; 65: 707-12.
38. BONGARTZ T, WARREN FC, MINES D, MATTESON EL, ABRAMS KR, SUTTON AJ: Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2009; 68: 1177-83.
39. NAM JL, WINTHROP KL, VAN VOLLENHOVEN RF *et al*.: Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010; 69: 976-86.
40. WOLFE F, MICHAUD K: Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum* 2007; 56: 2886-95.
41. WOLFE F, MICHAUD K: The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum* 2007; 56: 1433-9.
42. GEBOREK P, BLADSTROM A, TURESSON C *et al*.: Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; 64: 699-703.
43. ASKLING J, VAN VOLLENHOVEN RF, GRANATH F *et al*.: Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009; 60: 3180-9.
44. ASKLING J, BAECKLUND E, GRANATH F *et al*.: Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. *Ann Rheum Dis* 2009; 68: 648-53.
45. NICOLA PJ, CROWSON CS, MARADIT-KREMERS H *et al*.: Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 60-7.
46. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26: S35-61.
47. SIHVONEN S, KORPELA M, LAIPPALA P, MUSTONEN J, PASTERNACK A: Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. *Scand J Rheumatol* 2004; 33: 221-7.
48. DORAN MF, POND GR, CROWSON CS, O'FALLON WM, GABRIEL SE: Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum* 2002; 46: 625-31.
49. CHEHATA JC, HASSELL AB, CLARKE SA *et al*.: Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity. *Rheumatology* (Oxford) 2001; 40: 447-52.
50. WOLFE F, MITCHELL DM, SIBLEY JT *et al*.: The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
51. CARMONAL, DESCALZO MA, PEREZ-PAMPIN E *et al*.: All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. *Ann Rheum Dis* 2007; 66: 880-5.
52. BOOK C, SAXNE T, JACOBSSON LT: Prediction of mortality in rheumatoid arthritis based on disease activity markers. *J Rheumatol* 2005; 32: 430-4.
53. BARTELDS GM, WOLBINK GJ, STAPEL S *et al*.: High levels of human anti-human antibodies to adalimumab in a patient not responding to adalimumab treatment. *Ann Rheum Dis* 2006; 65: 1249-50.
54. 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* 2009; 68: 1739-45.