EXTENDED REPORT

Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease

Gerd R Burmester,[1] Remo Panaccione,[2] Kenneth B Gordon,[3] Melissa J McIlraith,[4] Ana P M Lacerda[5]

► Additional material is published online only. To view these files please visit the journal online (http://ard.bmj.com/content/early/recent).

[1]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany
[2]Department of Medicine, University of Calgary, Calgary, Canada
[3]Department of Dermatology, Northwestern University, Chicago, Illinois, USA
[4]Department of Rheumatology Medical Affairs, Abbott Laboratories, Rungis, France
[5]Immunology Medical Affairs, Abbott Laboratories, Sao Paulo, Brazil

Correspondence to
Professor G R Burmester, Department of Rheumatology and Clinical Immunology, Charité – University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany; gerd.burmester@charite.de

Accepted 9 April 2012
Published Online First 5 May 2012

ABSTRACT

Background As long-term treatment with antitumour necrosis factor (TNF) drugs becomes accepted practice, the risk assessment requires an understanding of anti-TNF long-term safety. Registry safety data in rheumatoid arthritis (RA) are available, but these patients may not be monitored as closely as patients in a clinical trial. Cross-indication safety reviews of available anti-TNF agents are limited.

Objective To analyse the long-term safety of adalimumab treatment.

Methods This analysis included 23 458 patients exposed to adalimumab in 71 global clinical trials in RA, juvenile idiopathic arthritis, ankylosing spondylitis (AS), psoriatic arthritis, psoriasis (Ps) and Crohn's disease (CD). Events per 100 patient-years were calculated using events reported after the first dose through 70 days after the last dose. Standardised incidence rates for malignancies were calculated using a National Cancer Institute database. Standardised death rates were calculated using WHO data.

Results The most frequently reported serious adverse events across indications were infections with greatest incidence in RA and CD trials. Overall malignancy rates for adalimumab-treated patients were as expected for the general population; the incidence of lymphoma was increased in patients with RA, but within the range expected in RA without anti-TNF therapy; non-melanoma skin cancer incidence was raised in RA, Ps and CD. In all indications, death rates were lower than, or equivalent to, those expected in the general population.

Conclusions Analysis of adverse events of interest through nearly 12 years of adalimumab exposure in clinical trials across indications demonstrated individual differences in rates by disease populations, no new safety signals and a safety profile consistent with known information about the anti-TNF class.

INTRODUCTION

Adalimumab, a fully human monoclonal antibody targeted against tumour necrosis factor (TNF), is indicated for the treatment of six immune-mediated inflammatory diseases: rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (Ps) and Crohn's disease (CD).

Because anti-TNF therapy suppresses the immune system,[1] serious infections are the most frequently reported serious adverse events of interest across indications for the anti-TNF drug class.[2] Given the role of TNF in mediating tumour growth,[1] risk of malignancy with anti-TNF therapy has been a concern, although studies in RA have not shown a consistent safety signal.[3] Complicating this risk assessment, there is substantial evidence that the chronic inflammation inherent in the conditions treated with anti-TNF therapy is itself associated with an increased potential for malignancy.[2 4 5]

Rates of adverse events in patients treated with anti-TNF agents can vary across therapeutic indications. Differences between populations (eg, disease-inherent risks, frequency of comorbidities and use of concomitant immunosuppressant drugs, including corticosteroids), may contribute to these differences.[6]

This analysis of the long-term safety profile of adalimumab through nearly 12 years of clinical trial exposure supplements registry safety data with well-monitored clinical trial data, highlights differences in adverse events between six patient groups, compares the risk of malignancy and mortality with the risk in the general population, examines temporal onset of adverse events and assesses two new events of interest—new onset/worsening of psoriasis and melanoma.

PATIENTS AND METHODS

Clinical trials

Data were derived from 71 adalimumab clinical trials, including randomised controlled trials, open-label trials and long-term extension studies conducted in Europe, North America, South America, Asia, Australia, New Zealand and South Africa, through 6 November 2010: 36 in RA, 3 in JIA, 4 in AS, 4 in PsA, 13 in Ps and 11 in CD. Safety data from adalimumab postmarketing surveillance were not included in this analysis to avoid limitations associated with voluntary reporting.[7]

Rates of serious adverse events of interest

Safety assessments included all adverse events that occurred after the first dose of adalimumab up to 70 days (five half-lives) after the last study dose. Serious adverse events were defined as fatal or immediately life-threatening; requiring inpatient

hospitalisation or prolonging existing hospitalisation; resulting in persistent or significant disability/incapacity; congenital anomaly; or requiring medical or surgical intervention to prevent a serious outcome. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, MedDRA version 13.1 (http://www.meddramsso.com).

Serious adverse events of interest were identified using predetermined search criteria. All patients underwent medical review by company doctors. Rates are reported as events per 100 patient-years (PYs). Kaplan–Meier analyses were used to evaluate the time to first serious infectious event and the time to first malignancy/lymphoma/non-melanoma skin cancer (NMSC) for each indication.

Malignancy and mortality data for patients versus the general population

Standardised incidence rates (SIRs) were calculated as the ratio of observed to expected number of cancers; 95% CIs for SIRs were calculated assuming that observed cancers followed a Poisson distribution.[8] The expected numbers of cancers, excluding NMSC, for SIR calculations were based on 5-year age-specific incidence rates from the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) database, 1993–2001 (http://www.seer.cancer.gov). No similar database is available for Europe, Australia or Canada so an assumption was made that patients from these territories could be pooled with subjects from the USA. The NCI SEER database does not include NMSC; therefore, NMSC rates were based on 10-year age-specific incidence rates from a NCI survey of eight locations in the USA from 1977 to 1978.[9]

Standardised mortality rates were calculated as the ratio of observed deaths to expected deaths. Expected rates were estimated based on country-specific, age- and sex-matched population data from the WHO for 1997–2006 (http://www.who.int/whosis/database/mort/table1.cfm).

RESULTS

Baseline characteristics and adalimumab exposure

Through 6 November 2010, adalimumab was administered to 23 458 patients, representing 36 730.5 PYs, a 23% increase in the number of adalimumab-treated patients and a 43% increase in PYs from a previous report.[10] Baseline characteristics were representative of patients for each condition (table 1). The majority of adalimumab exposure was in RA studies (table 1), with over 65% of the total exposure and 60% of the total patients exposed, compared with 71% of the total exposure and 65% of the total patients treated in the previous report.[10] The percentages of RA patients exposed >2 years (17.7%) and >5 years (11.7%) in this analysis were similar to the percentages in the 2009 Burmester dataset: 18.3% (2259/12 345) and 11.9% (1472/12 345), respectively.[10]

Serious adverse events

Serious infection

Serious infectious events (SIEs) were the most frequently reported serious adverse events across all six therapeutic indications, with the greatest rates of SIEs seen in patients with RA or CD (table 2).

The most commonly reported SIEs (rates >0.2 events/100 PYs) were cellulitis (0.3/100 PYs) and pneumonia (0.7/100 PYs) in RA, appendicitis (0.5/100 PYs) and herpes zoster (0.3/100 PYs) in JIA, urinary tract infection (0.4/100 PYs) in PsA, cellulitis (0.3/100 PYs) in Ps, and gastrointestinal tract abscess (1.6/100 PYs), gastroenteritis (0.3/100 PYs) and pneumonia (0.4/100 PYs) in CD. No SIE rate exceeded 0.2/100 PYs in AS studies.

Risk of SIE was generally stable across time for all indications (figure 1). The majority of patients with SIEs (70%, 846/1208) across all indications continued adalimumab therapy. Approximately 32% of patients with RA and 28% of patients with CD with SIEs permanently discontinued treatment, compared with 18–24% of patients with JIA, AS, PsA and Ps. The most common SIEs leading to adalimumab discontinuation (>1% of patients with SIEs who discontinued adalimumab) were pneumonia (6.6%), bacterial arthritis (2.8%), gastrointestinal tract abscess (2.6%) and cellulitis (1.7%).

Active tuberculosis

Incidence rates for active tuberculosis (TB), excluding tuberculin test conversions with no evidence of active disease, were comparable to the previous analysis (0.29/100 PYs).[10] No active TB

Table 1 Baseline characteristics of adalimumab-treated patients and adalimumab exposure by therapeutic indication

Characteristics	Rheumatoid arthritis	Juvenile idiopathic arthritis	Ankylosing spondylitis	Psoriatic arthritis*	Psoriasis	Crohn's disease	All patients
N	14 109	212	1684	837	3010	3606	23 458
Mean age, years	53.5	11.2	43.1	48.4	44.7	37.4	48.6
Mean disease duration, years	9.8†	3.9†	10.9	14.6†	19.3	11.1†	11.4†
Female, %	78.9	80.2	27.5	47.4	33.2	59.7	65.3
Receiving concomitant immunosuppressant agents, %	65.9	64.6	38.2	69.3	2.8	43.2	52.5
Receiving concomitant systemic steroids, %	64.4	53.3	35.5	26.8	4.9	34.6	48.7
From US sites, %	23.1	47.6	8.6	25.3	37.5	37.6	26.4
Exposure, PYs	23 942.6	604.9	1985.6	997.5	5061.8	4138.0	36 730.5
Median duration of exposure, years	0.7	2.6	0.4	0.4	0.7	0.5	0.6
Maximum duration of exposure, years	11.8	6.9	5.1	3.5	5.7	5.5	11.8
>2 Years of exposure, N (%)	2503 (17.7)	109 (51.4)	354 (21.0)	312 (37.3)	1228 (40.8)	703 (19.5)	5209 (22.2)
>5 Years of exposure, N (%)	1646 (11.7)	64 (30.2)	140 (8.3)	0	86 (2.9)	35 (1.0)	1971 (8.4)

*Psoriatic arthritis was the only indication with no new data from those previously reported.[10]
†Based on the following number of patients with available baseline disease duration information: rheumatoid arthritis, 13 739; juvenile idiopathic arthritis, 195; psoriatic arthritis, 819; Crohn's disease, 3238; and all patients, 22 685.
PYs, patient-years.

was seen in patients with JIA and AS. Across all indications, the rate of active TB in adalimumab clinical trials was 0.2/100 PYs, including cases from RA clinical studies before implementation of a tuberculin test screening programme.[11] Since latent TB infection screening and prophylaxis was implemented in 1998 and 1999, respectively, the rate has decreased from 1.5/100 PYs to 0.2/100 PYs.

Serious opportunistic infections

Twenty serious opportunistic infections, excluding TB and oral candidiasis, have been reported during adalimumab clinical trials (<0.1 events/100 PYs), 14 cases in patients with RA, four cases in patients with CD and two cases in JIA. The most common opportunistic infections were oesophageal candidiasis (n=3), and aspergillosis, Candida sepsis, coccidioidomycosis, cytomegalovirus infection, herpes zoster and nocardiosis (n=2 each). No serious opportunistic infections have been reported with adalimumab in AS, PsA or Ps clinical trials.

Serious demyelinating disorders, lupus-like syndrome, CHF

The incidence rates of serious demyelinating disorders, lupus-like syndrome and congestive heart failure (CHF) across all

Table 2 Incidence rates of serious adverse events of interest*

	Rheumatoid arthritis	Juvenile idiopathic arthritis	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	14 109	212	1684	837	3010	3606
Exposure, PYs	23 942.6	604.9	1985.6	997.5	5061.8	4138.0
Serious infections	4.6	2.0	1.4	2.8	1.7	6.7
Active tuberculosis	0.3	0	0	0.2	0.1	<0.1
Opportunistic infections	<0.1	0	0	0	0	<0.1
Demyelinating disorder	<0.1	0	<0.1	0	0	0.1
Lupus-like syndrome	<0.1	0	0.1	0	0	<0.1
CHF	0.2	0	0.1	0	<0.1	0
New onset/worsening of psoriasis	<0.1	0	<0.1	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	0.9	0	0.2	0.2	0.6	0.5
Lymphoma	0.1	0	<0.1	0.2	<0.1	<0.1
NMSC†	0.2	0	0.3	0.1	0.1	<0.1
Melanoma	<0.1	0	<0.1	0	0.2	0
Any AE leading to death	0.8	0	<0.1	0.3	0.2	0.1

*Rates in events/100 PYs.
†Only serious NMSC events.
AE, adverse event; CHF, congestive heart failure; NMSC, non-melanoma skin cancer; PYs, patient-years.

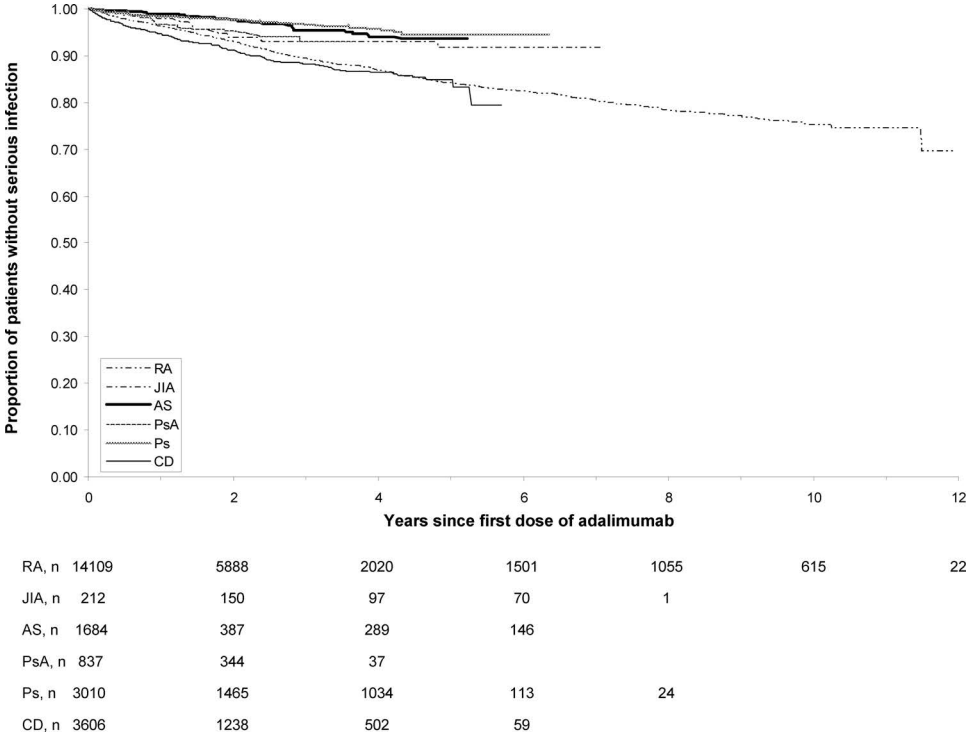


Figure 1 Time to first serious infection, by indication. AS, ankylosing spondylitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

indications were ≤0.1 events/100 PYs, with the exception of CHF in patients with RA, which was 0.2/100 PYs (table 2). Four serious CHF events were reported for the first time in patients with Ps. No cases of progressive multifocal leucoencephalopathy have been reported in adalimumab clinical trials.

Serious new onset/worsening of psoriasis

The incidence of new onset/worsening of psoriasis, classified as psoriasis or pustular psoriasis, was very low, ≤0.1 events/100 PYs (table 2). No serious new onset/worsening of psoriasis events were reported in JIA studies.

Malignancies

Rates of malignancies reported in adalimumab clinical trials across all indications were 0.7 events/100 PYs for malignancies excluding lymphoma and NMSC, 0.1/100 PYs for lymphoma, and 0.2/100 PYs for NMSC; these rates were generally similar to previously reported rates.[10] No malignancies were reported in JIA clinical trials with over 6 years of adalimumab exposure.

No cases of hepatosplenic T cell lymphoma were reported in any adalimumab study.

Kaplan–Meier analysis of time to first malignancy, for all malignancies excluding lymphoma and NMSC, did not show a marked difference between disease populations (figure 2). In all indications, the time to first lymphoma and time to first NMSC did not change with longer follow-up in this analysis. Risk of malignancy was generally low and remained stable over time.

Malignancy rates compared with data from the general population

SIRs for all malignancies were based on 294 malignancies, including lymphomas but excluding NMSC, observed in adalimumab trials across indications (figure 3). Compared with age- and sex-matched populations, the observed number of malignancies in each disease population was similar to the expected number in the reference population.

SIRs for lymphomas (figure 3) were based on 29 events from RA, one from AS, two from PsA, one from Ps and two from CD trials (all non-Hodgkin's lymphoma except for six cases of Hodgkin's lymphoma in RA studies). The number of lymphomas observed in RA studies was significantly greater than expected compared with a US-based age- and sex-matched population (SIR=2.74; 95% CI 1.83 to 3.93).

SIRs for NMSC (figure 3) were based on 184 events (134 basal cell carcinoma (BCC), 43 squamous cell carcinoma (SCC) and six type unclassified) from RA, six (three BCC and three SCC) from AS, six (four BCC and two SCC) from PsA, 40 (26 BCC and 14 SCC) from Ps and 22 (14 BCC, six SCC, and two not classified) from CD trials. For NMSC, patients with RA, Ps and CD had SIRs (95% CIs) >1, indicating a higher number of observed NMSC cases than expected in the general population.

SIRs for melanomas were based on 15 observed events reported in RA and eight events in Ps studies. The observed number of melanoma events was raised in Ps, with a SIR (95% CI) of 4.37 (1.89 to 8.61). In patients with RA, the SIR (95% CI) of 1.5 (0.84 to 2.47), did not show a higher incidence relative to the general population.

Mortality rates compared with data from the general population

Deaths were reported in each adalimumab clinical programme except JIA. For subjects treated with adalimumab in RA, AS and Ps clinical studies, the observed number of deaths was less than expected in an age- and sex-matched population. In PsA and CD studies, the observed number of deaths was similar to the number expected in the reference population (figure 4).

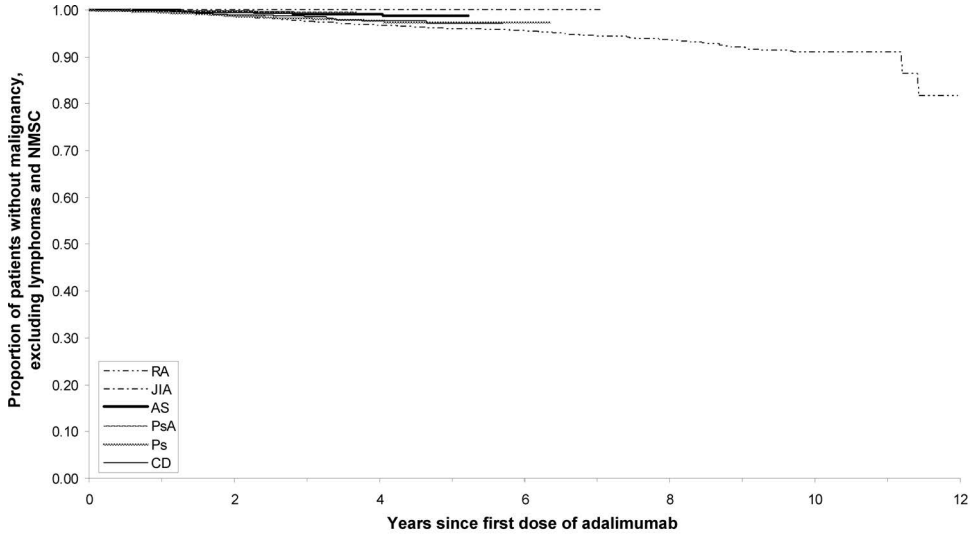


Figure 2 Time to first malignancy, other than lymphoma or non-melanoma skin cancer (NMSC), by indication. AS, ankylosing spondylitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

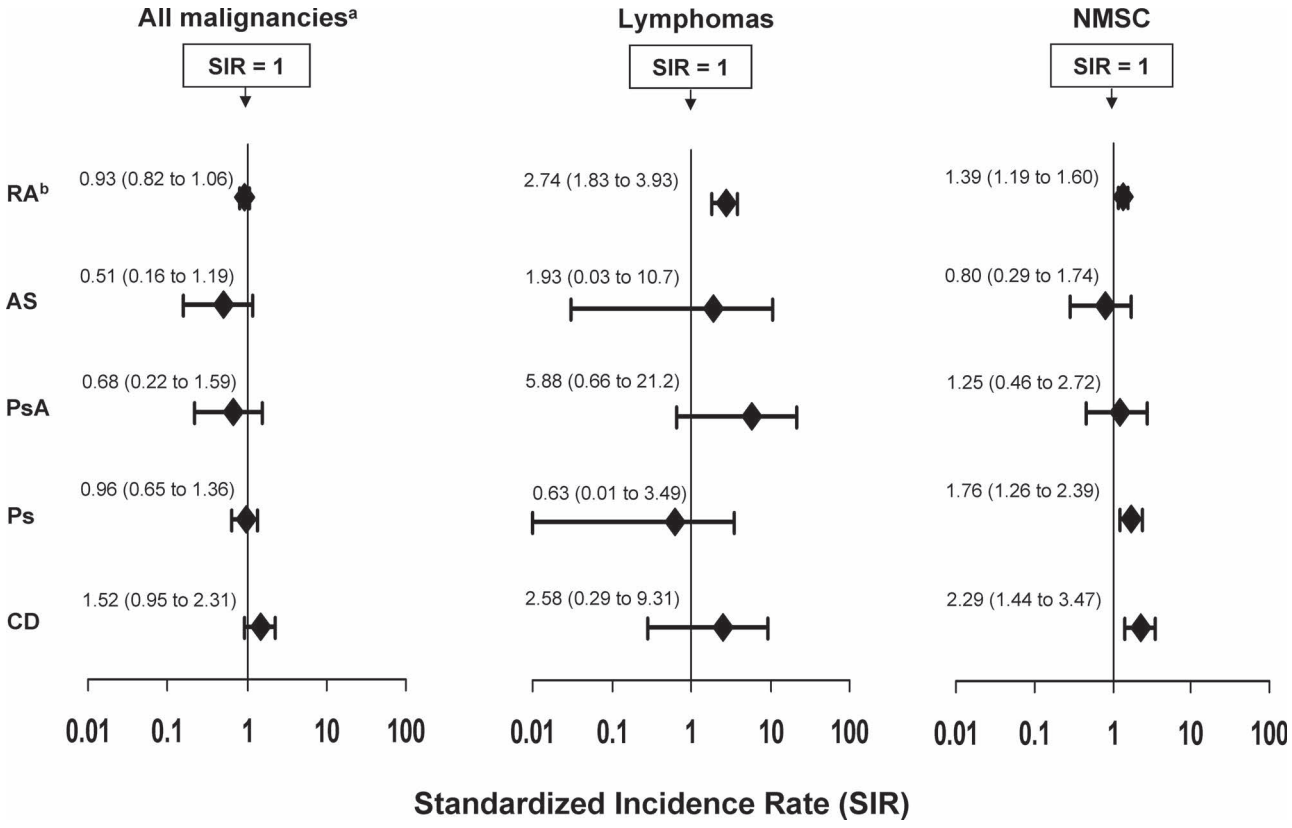


Figure 3 Standardised incidence rates (SIR, (95% CI)) for all malignancies excluding NMSC, lymphomas and NMSC for RA, AS, PsA, Ps and CD. No malignancies were observed for juvenile idiopathic arthritis. [a]All malignancies other than NMSC. [b]Based on data from 14 160 patients. AS, ankylosing spondylitis; CD, Crohn's disease; NMSC, non-melanoma skin cancer; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

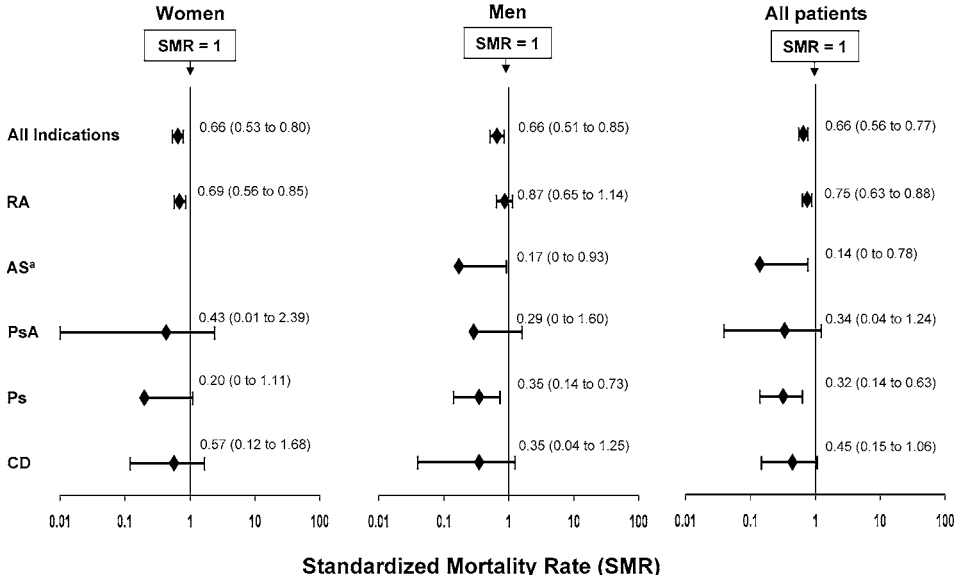


Figure 4 Standardised death rates (SMR, (95% CI)) for all indications, RA, AS, PsA, Ps and CD. No deaths occurred in juvenile idiopathic arthritis. [a]No deaths occurred among female patients with AS. AS, ankylosing spondylitis; CD, Crohn's disease; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

DISCUSSION

This safety analysis represents the largest safety database published for an anti-TNF drug across indications, with up to 12 years of adalimumab exposure. In this analysis, infections were the most frequently reported serious adverse events across all therapeutic indications, consistent with previous safety analyses of adalimumab trials[10 12–14] and other anti-TNF agents.[15] The overall rate of SIE and the stable risk of first SIE throughout adalimumab exposure is consistent with findings previously reported.[10] This differs somewhat from other risk estimates of anti-TNF therapy in RA, which suggest higher risk during the first 6–12 months of RA treatment.[16] Possible explanations include population and methodological differences between clinical trials and observational registries.

The incidence rate of SIEs in patients with RA in this analysis is consistent with data on anti-TNF treatments from various RA registries, including the British Society for Rheumatology Biologics Register (BSRBR),[6] the Spanish Society of Rheumatology drug registry (BIOBADASER),[17] the German Rheumatoid Arthritis Observation of Biologic Therapy Registry (RABBIT)[18] and the Swedish Biologics Register (ARTIS),[19] which have reported rates ranging from 3.8 to 6.4 events/100 PYs in patients receiving anti-TNF therapy including etanercept and infliximab.[6 15 18]

Risk factors for SIEs with anti-TNF agents include disease-inherent and individual patient characteristics. Analysis of the anti-TNF cohort of the BSRBR[6] as well as a population-based analysis from the Mayo Clinic[20] showed that age, disease activity, comorbidities (eg, diabetes, chronic obstructive pulmonary disease) and baseline corticosteroid use were significant predictors of SIEs in patients with RA, regardless of treatment with disease-modifying antirheumatic drugs or biological agents. Corticosteroid use is associated with infections in patients with RA,[21] and also in patients with CD, RA, AS, PsA and Ps, independently of anti-TNF use.[22–24] In our analysis, lower SIE rates were seen in AS, PsA, Ps and JIA, where many of the aforementioned risk factors are not present. Nevertheless, clinicians must consider patient comorbidities, concomitant treatment and infection history when actively monitoring their patients for infection while treating with anti-TNF agents.

Other serious adverse events of interest occurred infrequently. The rates of active TB in adalimumab clinical trials across indications were similar to the rates previously reported.[10] Opportunistic infections remain rare events. In the CORRONA registry for RA, a small risk of opportunistic infections was found with anti-TNF agents.[25] Vigilant patient monitoring for opportunistic infections with anti-TNF agents, now including Legionella and Listeria infections,[26] is recommended. Serious cases of demyelinating disorders, lupus-like syndrome, and CHF were uncommon, with low incidence rates generally remaining stable over time. Rates of serious CHF events remained as low as previously reported rates,[10] even with expansion of search criteria for events classified as CHF (eg, pulmonary oedema, hepatic congestion). Of the four patients with Ps with serious CHF events, three had two or more risk factors for CHF, including hypertension, hyperlipidaemia, diabetes mellitus, myocardial ischaemia and obesity. The fourth patient developed pulmonary oedema secondary to a near drowning. The incidence of serious new onset/worsening of psoriasis was low. Drug-induced psoriasis is uncommon, but appears to be immune system related, and was reported with the anti- TNF agents etanercept, infliximab and adalimumab,[27] as well as rituximab[28] and anakinra,[29] in patients treated for RA, AS, PsA, Ps and CD.

The overall rates of malignancy in adalimumab clinical trials were similar to rates expected in the reference population and consistent with rates previously published.[10 30] Additionally, the time to onset of a first malignant event appeared stable across all indications, suggesting no increased risk over time with prolonged treatment.

Incidence rates of lymphoma in patients with RA were greater than those expected in age- and sex-matched populations without RA; however, data demonstrate that the risk of lymphoma is raised in patients with RA as a consequence of the disease.[4 31 32] Chronic inflammatory activity is associated with lymphoma development, and patients with active RA are at greatest risk.[4] Data from ARTIS showed that the risk of lymphoma in patients with RA receiving anti-TNF agents, although higher than in the general population, was the same as in patients never treated with anti-TNFs.[31] Similarly, patients with RA in the Swedish Early Arthritis Register were found to have an inherent, nearly twofold increased risk for developing lymphomas during the first 10 years after diagnosis of RA, irrespective of treatment.[31] The greater rate of lymphoma observed during adalimumab trials in patients with RA is within the range that might be expected in a similar RA population not treated with anti-TNF therapy.

Increased SIRs for NMSC in patients with RA, Ps and CD suggest there is a small but significant increase risk of NMSC with adalimumab compared with the risk observed in the NCI survey. NMSC SIRs can vary according to the reference database used,[10] with SIRs generally greater using the NCI survey rather than other databases such as Arizona or Minnesota. This is probably because NCI demonstrated an increase in US skin cancer rates after the 1970s. Diagnosis of RA itself has been associated with a small risk of developing NMSC in a large national cohort of patients with RA.[33] Data from observational studies and meta-analysis suggest an increased risk of NMSC with anti-TNF use[30 34]; however, the increased risk was associated with combination methotrexate and anti-TNF therapy and not with anti-TNF monotherapy.[33] Patients with Ps and CD may also have an increased risk of NMSC. In Ps, use of high-dose psoralen and ultraviolet A light (PUVA) was associated with increased risk of NMSC.[35] In a large retrospective cohort of patients with CD, recent use (≤90 days) and persistent use (>365 days) of adalimumab and infliximab were associated with increased odds of developing NMSC.[36] However, it is not yet clear whether the underlying cause was related to detection bias, change in manifestation of NMSC or a true change in incidence.

Only the SIR in patients with Ps suggested an increased risk of melanoma with adalimumab. Most of these patients were exposed to other treatments such as ciclosporin, PUVA, retinoids and other immunosuppressants that have been associated with an increased risk of all skin malignancies.[37] Additionally, the incidence of melanoma is increasing worldwide.[38] Exposure to sunlight plus increased vigilance by dermatologists of these lesions might have contributed to these results. States of immune suppression have recently emerged as possible risk factors for melanoma.[39] In RA, data have suggested an increased risk of melanoma associated with anti-TNF therapy.[33 39] However, others have not found an increased risk of melanoma with anti-TNF agents at recommended doses for RA.[40 41]

The risk of mortality was not increased in adalimumab-treated patients compared with the reference population. Whether control of inflammation with adalimumab decreases certain mortality risks, such as cardiovascular disease[42–44] and use of steroids,[45 46] is yet to be determined. This hypothesis is supported by CORRONA RA registry data and a recently published meta-analysis showing that exposure to anti-TNF agents reduced non-infectious causes of mortality compared with patients not

exposed, with reduction in cardiac mortality appearing to be the major reason for this reduced risk.[42 47]

Several limitations exist in the interpretation of the findings of this analysis. Protocol-specified patient selection probably resulted in study populations with fewer comorbidities than the wider general patient population. Comparisons with other treatments could not be determined owing to lack of a control group in the long-term open-label periods. The reference population for malignancy SIRs was a US-based population, which may limit the generalisability of these global clinical trial results. Finally, patients in the adalimumab clinical trial programme were closely monitored at regular scheduled visits, which might have resulted in detection bias for adverse events.

The adalimumab safety data presented here provide important additional support for the long-term safety of adalimumab in six different immune-mediated inflammatory diseases, highlighting important differences among patient populations, and demonstrating stability of incidence rates over time with no new safety signals.

Acknowledgements The authors thank Kathleen V Kastenholz, PharmD, MS, of Abbott Laboratories, for medical writing and editing support in the development and revision of this manuscript. The authors also thank Joseph Beason, of Abbott Laboratories, for his statistical support.

Funding Abbott Laboratories sponsored the clinical trials and contributed to their design and data analysis.

Competing interests GRB has served as a consultant to Abbott Laboratories, Essex/Schering-Plough, Novartis and Roche and has received grants and honoraria from Abbott, Essex/Schering-Plough, Novartis, Roche, and Wyeth. RP has served as a consultant to Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Centocor, Elan, Ferring, GlaxoSmithKline, Procter and Gamble, Schering-Plough, Shire and UCB and has received grants from Abbott, Axcan, Bristol-Myers Squibb, Centocor, Elan, Millennium and Procter & Gamble and honoraria from Abbott Laboratories, Astra Zeneca, Byk Solvay, Centocor, Elan, Janssen, Procter and Gamble, Prometheus, Schering-Plough and Shire. KBG has received honoraria from and served as a consultant to Abbott Laboratories, Amgen, Centocor, Galderma, Pfizer, Merck and Lilly and has received grants from Abbott, Amgen, Centocor and Celgene. MJM and AL are employees of Abbott Laboratories and may hold stock or stock options.

Ethics approval National, regional, or investigative site ethics committees/institutional review boards, as appropriate.

Provenance and peer review Not commissioned; externally peer reviewed.

Correction notice This article has been corrected since it was published Online First. The unlocked logo has been added and figure 3 has been corrected.

REFERENCES

1. **Tracey D**, Klareskog L, Sasso EH, *et al*. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008;**117**:244–79.
2. **Hochberg MC**, Lebwohl MG, Plevy SE, *et al*. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum* 2005;**34**:819–36.
3. **Keystone EC.** Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis?: a review of long-term data. *J Rheumatol* 2011;**38**:1552–62.
4. **Baecklund E**, Iliadou A, Askling J, *et al*. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:692–701.
5. **Dommasch ED**, Abuabara K, Shin DB, *et al*. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2011;**64**:1035–50.
6. **Galloway JB**, Hyrich KL, Mercer LK, *et al.*; BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;**50**:124–31.
7. **Brewer T**, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999;**281**:824–9.
8. **Breslow NE**, Day NE. Statistical methods in cancer research: vol II – the design and analysis of cohort studies. International Agency for Research on Cancer. New York: Oxford University Press, 1987.
9. **Scotto J**, Fears TR, Fraumeni JF Jr. Incidence of nonmelanoma skin cancer in the United States. Bethesda, MD: US Dept of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 1983. NIH publication 83–2433.
10. **Burmester GR**, Mease P, Dijkmans BA, *et al*. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis* 2009;**68**:1863–9.
11. **Perez JL**, Kupper H, Spencer-Green GT. Impact of screening for latent TB prior to initiating anti-TNF therapy in North America and Europe. *Ann Rheum Dis* 2005;**64**(Suppl 3):265.
12. **Schiff MH**, Burmester GR, Kent JD, *et al*. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;**65**:889–94.
13. **Colombel JF**, Sandborn WJ, Panaccione R, *et al*. Adalimumab safety in global clinical trials of patients with Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1308–19.
14. **Leonardi C**, Papp K, Strober B, *et al*. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. *Am J Clin Dermatol* 2011;**12**:321–37.
15. **Curtis JR**, Jain A, Askling J, *et al*. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. *Semin Arthritis Rheum* 2010;**40**:2–14.e1.
16. **Askling J**, Dixon W. The safety of anti-tumour necrosis factor therapy in rheumatoid arthritis. *Curr Opin Rheumatol* 2008;**20**:138–44.
17. **Carmona L**, Descalzo MA, Perez-Pampin E, *et al.*; BIOBADASER and EMECAR Groups. 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.
18. **Listing J**, Strangfeld A, Kary S, *et al*. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005;**52**:3403–12.
19 **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.
20. **Doran MF**, Crowson CS, Pond GR, *et al*. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2294–300.
21. **Lacaille D**, Guh DP, Abrahamowicz M, *et al*. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;**59**:1074–81.
22. **Marehbian J**, Arrighi HM, Hass S, *et al*. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol* 2009;**104**:2524–33.
23. **Lichtenstein GR**, Feagan BG, Cohen RD, *et al*. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**:621–30.
24 **Grijalva CG**, Chen L, Delzell E, *et al*. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011;**306**:2331–9.
25 **Greenberg JD**, Reed G, Kremer JM, *et al.*; CORRONA Investigators. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;**69**:380–6.
26. **FDA Drug Safety Communication**: Drug labels for the tumor necrosis factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria, 2011. http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm. (accessed 14 December 2011).
27. **Ko JM**, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat* 2009;**20**:100–8.
28. **Dass S**, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. *Arthritis Rheum* 2007;**56**:2715–18.
29. **González-López MA**, Martínez-Taboada VM, González-Vela MC, *et al*. New-onset psoriasis following treatment with the interleukin-1 receptor antagonist anakinra. *Br J Dermatol* 2008;**158**:1146–8.
30. **Mariette X**, Matucci-Cerinic M, Pavelka K, *et al*. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systemic review and meta-analysis. *Ann Rheum Dis* 2011;**70**:1895–904.
31. **Hellgren K**, Smedby KE, Feltelius N, *et al*. Do rheumatoid arthritis and lymphoma share risk factors?: a comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. *Arthritis Rheum* 2010;**62**:1252–8.
32. **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.
33. **Chakravarty EF**, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol* 2005;**32**:2130–5.

34. **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.
35. **Stern RS**, Liebman EJ, Väkevä L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst* 1998;**90**:1278–84.
36. **Long MD**, Herfarth HH, Pipkin CA, *et al*. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010;**8**:268–74.
37. **Paul CF**, Ho VC, McGeown C, *et al*. Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol* 2003;**120**:211–16.
38. **Garbe C**, Leiter U. Melanoma epidemiology and trends. *Clin Dermatol* 2009;**27**:3–9.
39. **Vajdic CM**, McDonald SP, McCredie MR, *et al*. Cancer incidence before and after kidney transplantation. *JAMA* 2006;**296**:2823–31.
40. **Askling J;** ARTIS Study Group. Anti-TNF therapy and risk of skin cancer, data from the Swedish ARTIS registry 1998–2006 (EULAR abstract FRI0201). *Ann Rheum Dis* 2009;**68**(Suppl 3):423.
41. **Leombruno JP**, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009;**68**:1136–45.
42. **Barnabe C**, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;**63**:522–9.
43. **Listing J**, Strangfeld A, Kekow J, *et al*. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008;**58**:667–77.
44. **Szekanecz Z**, Kerekes G, Soltész P. Vascular effects of biologic agents in RA and spondyloarthropathies. *Nat Rev Rheumatol* 2009;**5**:677–84.
45. **Caplan L**, Wolfe F, Russell AS, *et al*. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. *J Rheumatol* 2007;**34**:696–705.
46. **Hanauer SB**, Feagan BG, Lichtenstein GR, *et al*.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
47. **Greenberg JD**, Kremer JM, Curtis JR, *et al*. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;**70**:576–82.

SUPPLEMENTAL FIGURE LEGENDS

Figure 1S. Time to first lymphoma, by indication. AS, ankylosing spondylitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Figure 2S. Time to first NMSC, by indication. AS, ankylosing spondylitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; NMSC, non-melanoma skin cancer; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Table S1. Adalimumab clinical trials[1]

ClinicalTrials.gov Registry Number	Primary Results Citation[2]
Rheumatoid Arthritis[3]	
NCT00195663	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(1):26–37.
NCT00195663	van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. J Rheumatol 2010 Nov;37(11):2237–46.
NCT00233571	
NCT00195702	Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical and functional outcomes with adalimumab (a human anti-TNF monoclonal antibody) in the treatment of patients with active rheumatoid arthritis on concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400–11.
NCT00195702	Keystone EC, Kavanaugh A, Weinblatt ME, et al. Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis. J Rheumatol. 2011 May;38(5):855–62. Epub 2011 Feb 1.
NCT00195650	
NCT00448383	Burmester GR, Ferraccioli G, Flipo RM, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008 Jan 15;59(1):32–41.
NCT00049751	
NCT00234845	

ClinicalTrials.gov Registry Number	Primary Results Citation[2]
NCT00650390	
NCT00235859	
NCT00235833	
NCT00647920	
NCT00649545	Haraoui B, Cividino A, Stewart J, et al. Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): results from the CanACT study. BMC Musculoskelet Disord 2011;12:261.
NCT00647491	
NCT00649922	
NCT00235872	
NCT00538902	
NCT00603993	
NCT00420927	
NCT00650156	
NCT00647270	
Juvenile Idiopathic Arthritis	
NCT00048542	Lovell DJ, Ruperto N, Goodman S, et al; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008 Aug 21;359(8):810–20.

ClinicalTrials.gov Registry Number	Primary Results Citation[2]
NCT00690573	
NCT00775437	
Ankylosing Spondylitis	
NCT00195819	Lambert RG, Salonen D, Rahman P, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2007 Dec;56(12):4005–14.
NCT00085644	Dougados M, Luo MP, Maksymowych WP, et al; ATLAS STUDY GROUP. Evaluation of the patient acceptable symptom state as an outcome measure in patients with ankylosing spondylitis: data from a randomized controlled trial. Arthritis Rheum. 2008 Apr 15;59(4):553–60.
NCT00478660	Rudwaleit M, Rødevand E, Holck P, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis. 2009 May;68(5):696–701.
NCT00667355	
Psoriatic Arthritis	
NCT00646386	
NCT00195689	Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702–9.
NCT00646178	

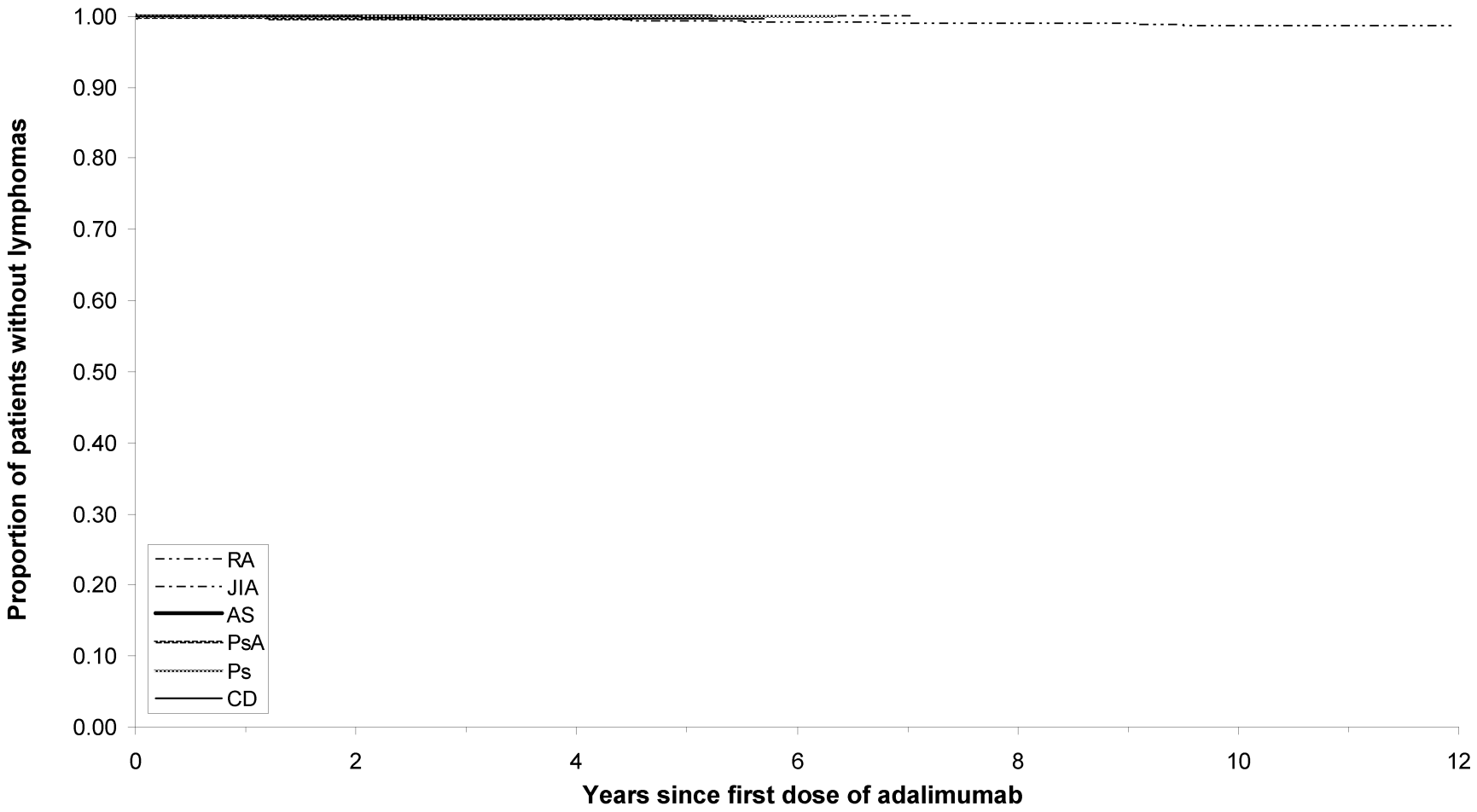
ClinicalTrials.gov Registry Number	Primary Results Citation[2]
NCT00235885	Rudwaleit M, Van den Bosch F, Kron M, et al. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. Arthritis Res Ther. 2010;12(3):R117.
Psoriasis	
NCT00645814	
NCT00646191	
NCT00645905	
NCT00645892	Larian A, Emer JJ, Gordon K, et al. Efficacy and safety of a second adalimumab treatment cycle in psoriasis patients who relapsed after adalimumab discontinuation or dosage reduction: a double-blind, randomized, placebo-controlled trial. Psoriasis Forum. 2011;17:88–96.
NCT00237887	Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol. 2008 Jan;58(1):106–15.
NCT00195676	
NCT00338754	
NCT00647400	
NCT00235820	Saurat JH, Stingl G, Dubertret L, et al; CHAMPION study investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008 Mar;158(3):558–66.

ClinicalTrials.gov Registry Number	Primary Results Citation[2]
NCT00574249	Thaçi D, Ortonne JP, Chimenti S, et al. A phase IIIb, multicentre, randomized, double-blind, vehicle-controlled study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone topical treatment in patients with moderate to severe psoriasis: the BELIEVE study. Br J Dermatol. 2010 Aug;163(2):402–11.
NCT00566722	Strober BE, Poulin Y, Kerdel FA, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. J Am Acad Dermatol. 2011 Apr;64(4):671–81.
NCT00735787	Leonardi C, Langley RG, Papp K, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. Arch Dermatol. 2011 Apr;147(4):429–36. Epub 2010 Dec 20.
NCT00513370	Papp K, Ho V, Teixeira H, et al. Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study. J Eur Acad Dermatol Venereol. Epub 2011 Oct 25. doi: 10.1111/j.1468-3083.2011.04225.x
Crohn's Disease	
NCT00055523	Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006 Feb;130(2):323–33.
NCT00077779	Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132:52–65.
NCT00055497	Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007 Sep;56(9):1232–9.

ClinicalTrials.gov Registry Number	Primary Results Citation[2]
NCT00195715	Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. Aliment Pharmacol Ther. 2010 Jun;31(12):1296–309.
NCT00105300	Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):829–38.
NCT00445939	
NCT00348283	
NCT00338650	Lichtiger S, Binion DG, Wolf DC, et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther. 2010 Nov;32(10):1228–39.
NCT00409617	Löfberg R, Louis E, Reinisch W, et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. Inflamm Bowel Dis. 2012 Jan;18(1):1–9. Epub 2011 Feb 23 doi: 10.1002/ibd.21663.
NCT00445432	
NCT00427921	

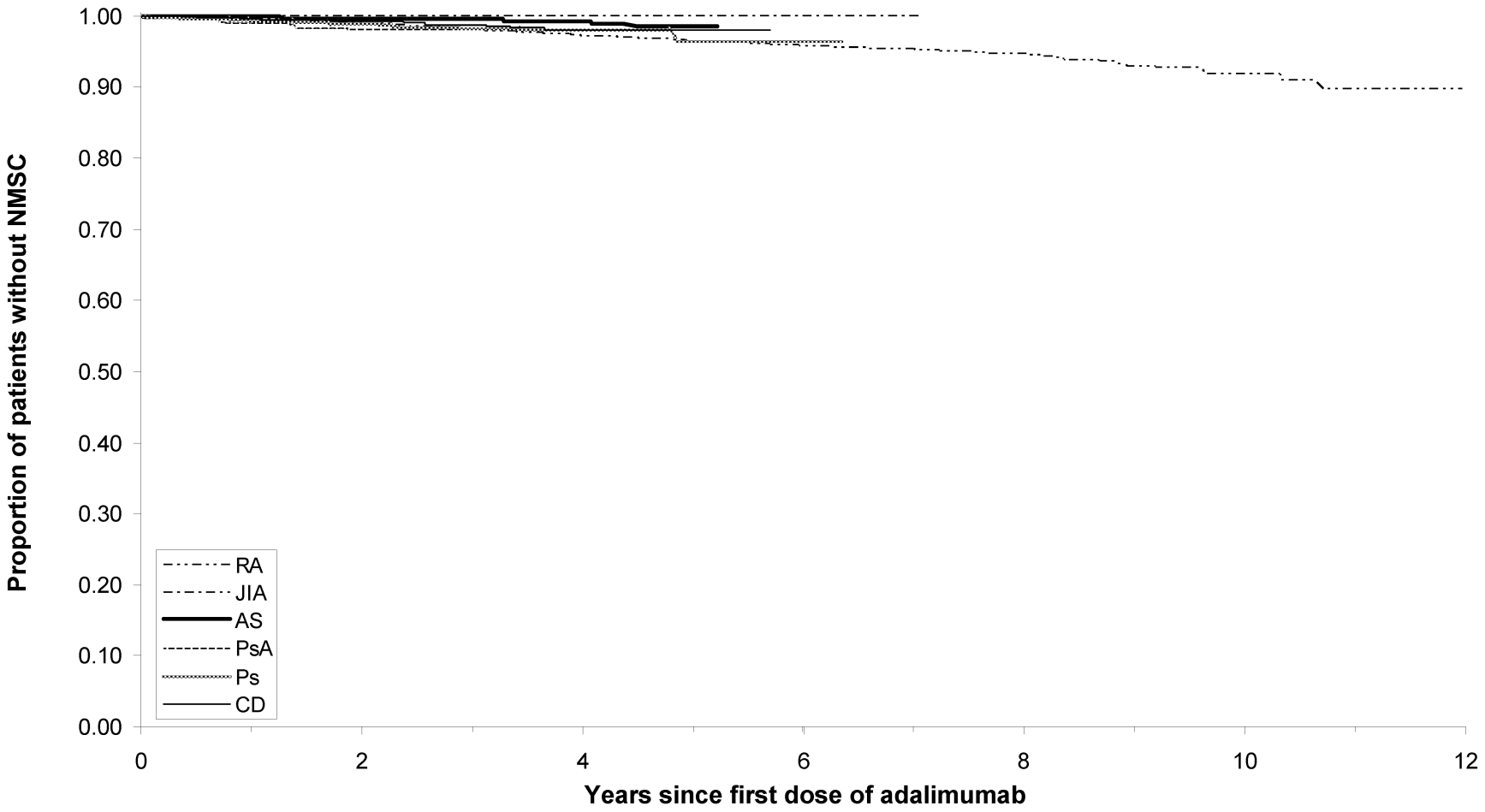
[1] Patients enrolled in clinical trials had confirmed diagnoses and active disease. Patients who were excluded had underlying active infection at baseline; a current history of active tuberculosis; a history of malignancy other than carcinoma in situ of the cervix or successfully treated, non-metastatic squamous or basal cell skin carcinoma; or a history of significant uncontrolled cardiac, renal, hepatic, neurologic, psychiatric, endocrinologic, or metabolic disease.
[2] Results may be available at www.clinicaltrials.gov.
[3] 14 rheumatoid arthritis studies were conducted prior to www.clinicaltrials.gov registration availability.

Figure 1S



RA, n	14109	6029	2175		686	26
JIA, n	212	152	104			
AS, n	1684	391	299			
PsA, n	837	353	38			
Ps, n	3010	1477	1054	117	24	
CD, n	3606	1279	540	63		

Figure 2S



RA, n	14109	6002	2123	1591	1119	628	23
JIA, n	212	152	104	75	1		
AS, n	1684	390	297	151			
PsA, n	837	351	38				
Ps, n	3010	1468	1038	111	23		
CD, n	3606	1274	532	60			