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DOI:
[10.1111/bjd.17084](https://doi.org/10.1111/bjd.17084)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Leonardi, C., Papp, K., Strober, B., Thaçi, D., Warren, R. B., Tying, S., Arian, D., Karunaratne, M., & Valdecantos, W. C. (2019). Comprehensive Long-Term Safety of Adalimumab from Eighteen Clinical Trials in Adult Patients With Moderate to Severe Plaque Psoriasis. *The British journal of dermatology*, 180(1), 76-85. <https://doi.org/10.1111/bjd.17084>

Published in:

The British journal of dermatology

Citing this paper

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KIM PAPP (Orcid ID : 0000-0001-9557-3642)

DR BRUCE E STROBER (Orcid ID : 0000-0002-8394-2057)

Article type : Original Article

Comprehensive Long-Term Safety of Adalimumab from Eighteen Clinical Trials in Adult Patients With Moderate to Severe Plaque Psoriasis

C. Leonardi,¹ K. Papp,² B. Strober,³ D. Thaçi,⁴ R. B. Warren,⁵ S. Tying,⁶ D. Arian,⁷ M. Karunaratne,⁷ W. C. Valdecantos⁷

¹St. Louis University Department of Dermatology, St. Louis, MO, USA; ²Probit Medical Research and K Papp Clinical Research, Waterloo, ON, Canada; ³University of Connecticut Department of Dermatology and Probit Medical Research, Farmington, CT, USA;

⁴Comprehensive Center Inflammation Medicine, University of Lübeck, Lübeck, Germany;

⁵Dermatology Centre, Salford Royal NHS Foundation Trust, NIHR Manchester Biomedical Research Centre, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK, M13 9PT; ⁶University of Texas Health Science Center at Houston, Department of Dermatology, Houston, TX, USA; ⁷AbbVie Inc., North Chicago, IL, USA

Corresponding author:

Address: Dr Craig Leonardi, MD
Central Dermatology
1034 S. Brentwood Blvd #600
St. Louis, MO 63117

Phone: 314-721-5565

E-mail: Craig.Leonardi@centralderm.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17084

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Funding

AbbVie Inc. (North Chicago, IL, USA) funded the research and had input into the study design, data analysis and interpretation, manuscript preparation and approval, and publication decisions.

Disclosures

Craig Leonardi has received research funding and/or served as a consultant for Actavis, AbbVie, Amgen, Celgene, Coherus, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB, and Wyeth. Kim Papp has served as a consultant for AbbVie, Amgen, Anacor, Astellas, Astra-Zeneca, Baxter, Boehringer Ingelheim, Celgene, Coherus, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GSK, Janssen, Kirin, Kyowa, Leo, Meiji Seika Pharma Co., Ltd., Merck (MSD), Mitsubishi Pharma, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Roche, Serono, Takeda, and UCB; served as a speaker for AbbVie, Amgen, Astellas, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck (MSD), Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Serono, and UCB; served on an advisory board for AbbVie, Amgen, Astellas, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Merck (MSD), Mylan, Novartis, Pfizer, and UCB; served on the data and safety monitoring board for Astellas and Kyowa; served on steering and/or publication committees for Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer; served as a scientific officer for AbbVie and Anacor; received grant/research support from AbbVie, Amgen, Anacor, Astellas, Astra-Zeneca, Baxter, Boehringer Ingelheim, Celgene, Coherus, Dermira, Eli Lilly,

Forward Pharma, Galderma, Genentech, GSK, Janssen, Kyowa, Leo, Merck (MSD), Mitsubishi Pharma, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Roche, Serono, Takeda, and UCB; and received honoraria from AbbVie, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Eli Lilly, Forward Pharma, Galderma, Genentech, Janssen, Kyowa, Meiji Seika Pharma Co., Ltd., Merck (MSD), Mitsubishi Pharma, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Serono, Takeda, and UCB. Honoraria paid by AbbVie were for activities that were unrelated to authorship. Bruce Strober has served as a consultant for AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene (paid to University of Connecticut), Dermira, GlaxoSmithKline, Janssen, Leo, Eli Lilly, Maruho, Medac, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, Sun, Stiefel/GlaxoSmithKline, UCB, and Valeant; is the scientific director for the CORRONA Psoriasis Registry; and has received grant support to the University of Connecticut for Fellowship Program from AbbVie and Janssen.

Diamant Thaçi has received honoraria from AbbVie, Almiral, Amgen, Astellas, Biogen Idec, Boehringer Ingelheim, Celgene, Dignity, Forward Pharma, Galderma, GSK, Janssen-Cilag, Leo Pharma, Eli Lilly, Maruho, Medac, MedImmune, Merck Sharp & Dome, Merck-Serono, Novartis, Regeneron, Sandoz, Sanofi-Aventis, Takeda, Pfizer, and UCB for participation on advisory boards, as a speaker, and for consultancy; and received research grants from AbbVie, Biogen Idec, Leo Pharma, and Pfizer.

Richard B. Warren has served as a consultant for/received research funding from AbbVie, Amgen, Almirall, Boehringer Ingelheim, Celgene, Pfizer, Leo, Janssen, Medac, Novartis, Eli Lilly, UCB, and Xenoport.

Stephen Tying has served as a clinical investigator for studies sponsored by AbbVie and is a speaker and consultant for AbbVie.

Dilek Arikan and Wendell Valdecantos are employees of AbbVie and may own AbbVie stock/stock options.

Mahinda Karunaratne is a former employee of AbbVie and may own AbbVie stock/stock options.

What's Already Known About This Topic?

- The long-term safety of adalimumab has been established in >23,000 patients in clinical trials across multiple indications. A previous comprehensive safety analysis of long-term adalimumab clinical data in psoriasis from 13 clinical trials demonstrated a favourable safety profile for adalimumab in psoriasis.

What Does This Study Add?

- Five additional adalimumab clinical trials in psoriasis have been completed since the November 2009 analysis. This comprehensive long-term integrated analysis of adalimumab safety in 3727 patients with psoriasis enrolled in 18 clinical studies found no new safety signals and was comparable to the previous safety report. The adverse event rates remained stable and consistent with currently approved labelled indications over increased adalimumab exposure time.

Summary

Background Adalimumab (Humira[®]; AbbVie Inc., USA) is a fully human monoclonal antibody specific for tumour necrosis factor- α approved to treat adults with moderate-to-severe chronic plaque psoriasis.

Objective To assess long-term safety for patients with psoriasis receiving adalimumab in clinical studies

Methods Adalimumab safety data from adults with psoriasis who received ≥ 1 adalimumab dose in 18 clinical trials were evaluated. Adalimumab was delivered subcutaneously in all treatment regimens. Treatment-emergent adverse events (AEs) were collected from the first dose to 70 days after last dose or cutoff date (December 31, 2015). AE incidence rates were expressed as events per 100 patient-years (E/100 PYs) of adalimumab exposure. Standardized incidence ratios (SIRs) for malignancies and standardized mortality ratios (SMRs) were calculated.

Results Cumulative exposure was 5429.7 PYs in 3727 patients. Overall, there were 16,536 AEs (304.6 E/100 PYs). Most common AEs were nasopharyngitis, upper respiratory infection, and headache (23.7, 12.9, and 7.9 E/100 PYs, respectively). Incidence rates for serious infections, tuberculosis, and opportunistic infections were 1.8, 0.3, and 0.02 E/100 PYs, respectively.

Incidence of malignancy excluding non-melanoma skin cancer (NMSC) was 0.8 E/100 PYs (SIR=0.86; 95% CI, 0.58–1.23). Incidences of NMSC and melanoma were 0.6 and 0.2 E/100 PYs, respectively. SIR was 1.55 (95% CI, 1.10–2.13) for NMSC and 3.04 (95% CI, 1.11–6.62) for melanoma. SMR was 0.34 (95% CI, 0.16–0.65).

Conclusions AE rates remained stable in this analysis of patients with psoriasis receiving adalimumab; no new safety signals were identified compared with earlier analyses.

ClinicalTrials.gov registry numbers: NCT00645814, NCT00645905, NCT00338754, NCT00237887, NCT00235820, NCT01646073, NCT01644396, NCT02016482, NCT02533375, NCT00646191, NCT02533375, NCT00645892, NCT00195676, NCT00647400, NCT00566722, NCT00513370, NCT02196701, NCT00735787

Introduction

Long-term safety data are particularly important for therapies used over extended periods of time for treatment of chronic conditions such as psoriasis, an immune-mediated inflammatory skin disease that affects 2% to 4% of the population in Western countries.¹ Extended exposure to immunosuppressants for treatment of psoriasis potentially could lead to serious adverse events, including infections and malignancies.^{2,3}

Adalimumab (Humira®; AbbVie Inc., North Chicago, USA), a fully human monoclonal antibody specific for tumour necrosis factor- α (TNF- α), is indicated for the treatment of adults with moderate to severe chronic plaque psoriasis. Additionally, adalimumab is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis in United States), Crohn's disease, ulcerative colitis, hidradenitis suppurativa, uveitis, paediatric Crohn's disease in the United States and Europe, and severe chronic paediatric plaque psoriasis in Europe. Concerns have been raised about the long-term effects of TNF- α inhibitors such as adalimumab on the immune system and its ability to defend against serious infections such as tuberculosis (TB).⁴

The long-term safety of adalimumab has been established in >23,000 patients in clinical trials across multiple indications.⁵ A previous comprehensive safety analysis of long-term adalimumab clinical data in psoriasis from 13 clinical trials (data cutoff November 6, 2009) that

included 3010 patients with 4844.7 patient-years (PYs) of exposure revealed no evidence of cumulative toxicity;⁶ since then, 5 additional adalimumab clinical trials in psoriasis have been conducted. Here we provide an updated analysis of the safety of adalimumab in adult patients with moderate to severe plaque psoriasis using the most recent data cutoff (December 31, 2015).

Methods

Study Design

This analysis included data from 18 clinical studies in adult patients with psoriasis (N=3727): two phase 2, double-blind, placebo-controlled studies; one phase 2/3 double-blind placebo-controlled study; five phase 3 studies; four extension studies; four phase 3b studies; and two phase 4 studies (**Supplementary Table 1**).

The main inclusion and exclusion criteria for most of the studies have been previously published.⁷⁻¹⁹ Briefly, included patients were aged ≥ 18 years with a diagnosis of moderate to severe psoriasis for ≥ 6 months. Patients with prior treatment with anti-TNF- α medications were excluded, except in extension studies, in which adalimumab could be continued, and in study W10-151, in which prior anti-TNF- α antagonists were permitted. Prior treatment with anti-TNF- α antagonists was not an exclusion criterion for study M10-238, but these treatments were discontinued before study medication administration. Detailed inclusion and exclusion criteria for all 18 clinical studies are listed in **Supplementary Table 2**. Adalimumab was administered subcutaneously in all treatment regimens. Dosing regimens are summarized in **Supplementary Table 1**.

The individual studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and the principles of the Declaration of

Helsinki that were in place at the time the studies were conducted. The study protocols were approved by an independent ethics committee or institutional review board at each site, and all patients provided written informed consent.

The studies could be stopped if continued exposure to the study medication represented a significant risk to patients, as assessed by the sponsor or the investigator. Additional reasons for termination by the sponsor included safety concerns, unsatisfactory enrolment (quantity or quality), inaccurate or incomplete data collection, falsification of records, and failure to adhere to the protocol.

Methodology for the Integrated Analysis

The analysis examined the all adalimumab treatment set (AAT), defined as all patients from all studies in the adalimumab psoriasis clinical development program who received ≥ 1 dose of adalimumab as part of any treatment regimen. Treatment-emergent adverse events (AEs) were collected from the first dose to 70 days after the last dose or the cutoff date (December 31, 2015) and coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1. AE reports were acquired automatically using lower-level group terms from the MedDRA; this differed from the methodology of the previous 2009 comprehensive safety analysis in which queries used MedDRA-defined preferred term group searches and company-defined preferred terms, requiring manual adjudication. AE incidence rates were expressed as events per 100 patient-years (E/100 PYs) of exposure to adalimumab. Each patient was monitored by the investigator for clinical and laboratory evidence of AEs on a routine basis throughout the studies. AEs that were life-threatening, resulted in death, required hospitalization or prolonged a hospital stay, or resulted in a congenital anomaly or other medically important events were reported as

serious AEs by the investigator or the sponsor. AEs commonly associated with adalimumab use (frequency $\geq 1\%$ to 10%) were assessed and included nausea; fatigue; injection site reactions including erythema, pain, and pruritis; pyrexia; bronchitis; herpes zoster; influenza; nasopharyngitis; oral herpes; pneumonia; sinusitis; upper respiratory tract infection; urinary tract infection; antinuclear antibody positive; arthralgia; rheumatoid arthritis; headache; cough; pruritus; and rash. Data from study M14-193 (generalized pustular psoriasis study; planned enrolment, n=10; patients enrolled as of December 31, 2015, n=5; patients receiving adalimumab as of December 31, 2015, n=4) were excluded from most analyses, except for the standardized incidence ratios (SIRs) for malignancies and the standardized mortality ratios (SMRs).

The SIRs for malignancies were calculated as a ratio of observed to expected number of malignancies. The expected numbers of cancers, excluding non-melanoma skin cancer (NMSC), were based on incidence rates from the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) database from 2000 to 2007.²⁰ In situ cancers were not included in the NCI SEER incidence rates; therefore, they were excluded from SIR analysis. The NCI SEER database did not include NMSC; therefore, NMSC rates were taken from a 1977–1978 NCI survey in the United States,²¹ the most recent available published data.

The SMRs were calculated as the ratio of observed to expected deaths. Expected deaths were estimated based on patient-years of treatment from the World Health Organization (WHO) most recent age- and country-specific mortality tables available at the time of analysis (years 1997–2006).²²

Results

As of December 2015, 3727 patients with psoriasis received adalimumab and had a cumulative exposure of 5429.7 PYs. Average exposure per patient was approximately 1.5 PYs (17.5 patient-months). Maximum duration of exposure to adalimumab was approximately 5.5 years (>288 weeks, n=19; **Fig. 1**). Baseline demographics and clinical characteristics were similar between the 2009 and 2015 data sets (**Table 1**). Mean age of patients was 44.7 years, most patients were white, and the mean (SD) duration of psoriasis was 19.0 ± 11.7 and 18.5 ± 11.7 years at baseline in the 2009 and 2015 data sets, respectively. Patient disposition is summarized in **Supplementary Table 3**.

Treatment-Emergent Adverse Events

In the 3723 patients included in safety analysis, there were 16,536 AEs, yielding an incidence of 304.6 E/100 PYs; 3798 events (70.0 E/100 PYs) were related to adalimumab as assessed by an investigator, and 269 events (5.0 E/100 PYs) led to discontinuation. Events leading to discontinuation included worsening of psoriasis (0.3 E/100 PYs), prostate cancer (0.1 E/100 PYs), and psoriatic arthropathy (0.1 E/100 PYs); all other events leading to discontinuation had an incidence of <0.1 E/100 PYs.

Incidence rates of the most frequently reported AEs (occurring in $\geq 5\%$ of patients) were generally comparable to the 2009 data set (**Table 2**). The most frequently reported AEs were nasopharyngitis, upper respiratory tract infections, and headache.

Treatment-Emergent Adverse Events of Interest

Overall, rates of serious AEs, serious infections, and malignancies remained stable with increasing adalimumab exposure and were similar for the 2009 and 2015 data sets (**Figs 2A–C**). Increases in incidence rates for single 24-week periods were observed in both data sets for serious AEs (weeks >192–216 due to umbilical hernia, chest discomfort, humerus fracture, malignant melanoma, rectal adenocarcinoma, chronic kidney disease, urinary incontinence, nasal septum deviation, and in the 2015 data set only, abdominal adhesions, osteoarthritis, procedural pain, pneumonia, post-procedural infection), serious infections (weeks >216–240 due to hepatitis C and osteomyelitis), and malignancies (weeks >192–216 due to malignant melanoma and rectal adenocarcinoma). There was an increase in malignancies in the 2015 AAT population compared with the 2009 AAT population during weeks 240–264 (1.9% [2 events of basal cell carcinoma] vs 0 respectively; **Fig. 2C**).

At the cutoff date of December 31, 2015, serious AEs occurred at a rate of 8.4 E/100 PYs and serious infections occurred at a rate of 1.8 E/100 PYs (**Table 4**). The most common serious infections were pneumonia (0.3 E/100 PYs) and cellulitis (0.2 E/100 PYs); all others occurred at a rate of ≤ 0.1 E/100 PYs.

There were 43 malignancies excluding NMSC reported through 2015 (0.8 E/100 PYs). Ten events of melanoma were reported as of December 31, 2015, compared with 9 events of melanoma in the 2009 data set. Six patients with melanoma had a history of ultraviolet A (UVA, n=1) or B (UVB, n=3) treatment and/or significant sun exposure (1 patient was a farmer with years of excessive sun exposure, 1 patient had significant sun exposure and developed cataracts and recent basal cell carcinoma, and 1 patient had a history of extensive sunbathing). One patient

had a family history of metastatic melanoma. Five patients who developed melanoma had a duration of adalimumab treatment of <6 months.

The incidence of malignancies excluding NMSC in patients treated with adalimumab for all body sites combined was comparable to the expected rate of diagnosed cancer for this demographic population, with an SIR of 0.86 (95% CI, 0.58–1.23; **Fig. 3**).

There were 33 events of NMSC reported through 2015 (0.6 E/100 PYs). In the 2009 analysis, 34 cases of NMSC were reported; the difference in the number of NMSC cases could be the result of the application of new search strategies to identify all potential reports. Specifically, one event with the preferred term of neoplasm skin and lower-level term of skin growth was included in the 2009 analysis but was not part of the NMSC search and did not meet the criteria for the 2015 analysis. The incidence of NMSC was elevated in patients treated with adalimumab, with a SIR of 1.55 (95% CI, 1.10–2.13; **Fig. 3**).

Nine fatal AEs and 8 deaths (1 death resulted from 2 fatal AEs) were reported in 2009.⁶ One additional death from congestive heart failure occurred since then: an Asian male aged 38 years experienced congestive heart failure, severe myocarditis, pulmonary infection, and arrhythmia. The patient had no known risk factors, and this event was considered related to adalimumab treatment (adalimumab 40 mg every other week; exposure, 114 days). The SMR was 0.34 (95% CI, 0.16–0.65) for the 2015 data set; 0.38 (95% CI, 0.16–0.74) for men and 0.19 (95% CI, 0.00–1.06) for women. Based on these data, the patients exposed to adalimumab in psoriasis clinical trials had mortality rates no greater than the patients in the WHO database used for comparison.

There were 16 reported events of TB (0.3 E/100 PYs); 9 were active (0.2 E/100 PY) and 7 were latent (0.1 E/100 PY). Three patients had a positive purified protein derivative (PPD) test

at screening. Since 2009, there were 2 new cases of active TB and 7 new cases of latent TB. The 2 new cases of active TB were reported from the study in China, and 4 of 7 new cases of latent TB were reported from the study in Russia.

Additionally, the rate of allergic reactions was higher for the 2015 data set versus the 2009 data set (3.9 vs 1.1 E/100 PYs). Rates of opportunistic infection were higher in the 2009 data set; however, the 2015 analysis did not include oral candidiasis. Only 1 event (<0.1 E/100 PYs) of opportunistic infection (excluding TB and oral candidiasis) was reported in the 2015 data set. Eleven events of oral candidiasis (0.2 E/100 PYs) were reported in the 2015 data set (**Table 4**). Lupus-like reaction and systemic lupus erythematosus incidence was 0.04 E/100 PYs in the 2015 data set (**Table 4**); cutaneous lupus was observed in two patients.

The most common AE of interest was injection-site reactions (11.0 E/100PYs). Other AEs of interest included depression (1.5 E/100PYs) and anxiety (1.2 E/100PYs); 31 out of 74 patients with depression had previous history of depression and/or anxiety; 1 patient committed suicide (0.02 E/100PYs). Additional AEs of interest included herpes zoster (0.8 E/100PYs; 7/458 events of herpes zoster in patients ≥ 60 years old [1.0 E/100PYs] vs 37/3265 events in patients <60 years old [0.8 E/100PYs]), and weight loss (0.2 E/100PYs; **Table 4**).

Discussion

This comprehensive long-term safety analysis of 3727 patients with a cumulative exposure of 5429.7 PYs to adalimumab identified no new safety signals in patients with psoriasis enrolled in 18 adalimumab clinical trials compared with the 2009 analysis of 13 clinical trials. The rates of AEs and AEs of interest remained stable, including serious AEs, infectious AEs, fatal AEs, and malignancies. Results from the 18 clinical trials included in this analysis are comparable with

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observations from the ongoing, 10-year, real-world adalimumab psoriasis ESPRIT registry,²³ and AE rates were consistent with other currently approved labelled indications for adalimumab over increased adalimumab exposure time.

The incidence rate of serious infection (1.8 E/100 PYs) reported in this analysis was within the range of serious infections rates of 1.0 E/100 PYs²³ and 1.97 E/100 PYs²⁴ reported in patients with psoriasis receiving adalimumab in 2 real-world registries.

The overall incidence rates of malignancies excluding NMSC remained stable from 2009 to 2015 (0.7 and 0.8 E/100 PYs, respectively). This is consistent with the rates of malignancies excluding NMSC reported for infliximab (0.79 E/100 PYs) and other biologics (0.49–0.73 E/100 PYs) or non-biologics (0.46–0.84 E/100PYs) reported by real-world registries.^{25,26} An increase in malignancies in the 2015 vs 2009 AAT populations during weeks 240–264 (1.9% vs 0) was because of 2 events of basal cell carcinoma.

While the SIRs for melanoma and NMSC were elevated in patients with psoriasis (3.01; 95% CI, 1.11–6.62 and 1.55; 95% CI, 1.10–2.13, respectively) who participated in the adalimumab studies, the incidence rates remained stable from 2009 to 2015. There were 9 events of melanoma (0.2 E/100 PYs) in the 2009 data set and 10 events (0.2 E/100 PYs) in the 2015 set resulting from reclassification of lentigo maligna as a melanoma in the 2015 analysis. Half of these patients had adalimumab exposure that was likely too short (<6 months) for a causal relationship. All 10 melanoma cases reported in this study had at least one confounding factor. Psoriasis patients over their lifetime, more than the average unaffected population, tend to seek natural ultraviolet exposure for its therapeutic benefits. Of the 10 patients who developed melanoma, 3 had significant sun exposure. Other patients with melanoma had exposure to UVA or UVB. More frequent skin examinations by dermatologists in a clinical trial setting could lead

to increased chance of melanoma detection and could be an additional confounding factor when comparing the melanoma incidence with the NCI SEER general population rate. Melanoma cases could be potentially underreported in the NCI SEER database because data are primarily collected from hospital reports, thus raising the SIRs in this study.²⁷ Also, per NCI SEER, rates of new cases of melanoma of the skin have been rising on average 1.4% each year over the last decade.

Because dermatologists have expertise in skin-related malignancies, NMSC diagnoses may be more likely in patients being treated for psoriasis, whereas SIRs may reflect comparison with general surveillance. Additionally, the elevated SIR for NMSCs may be attributable to the severity of the disease and/or prior treatment. The risk of NMSC increased with increasing severity of psoriasis in a study of patients in the United States.²⁸ Psoriasis treatment (including UVB, oral psoralen and UVA, and cyclosporine) has been associated with an increased risk of NMSC.^{29,30} However, it is unclear if long-term treatment with TNF- α inhibitors directly increase the risk of cutaneous malignancies such as malignant melanoma or non-melanoma skin cancers; more definitive studies may be needed to further evaluate the effects of TNF- α inhibition on malignancies.

There were 8 deaths in the 2009 analysis. We report one additional death from congestive heart failure that occurred since 2009. The mortality rate among patients exposed to adalimumab was no greater than the mortality rate among patients in the general population (SMR, 0.34 [95% CI, 0.16–0.65]). However, inclusion and exclusion criteria used in the clinical trials may affect the mortality rates, and the shorter durations of the clinical trials compared with the general population data may also affect the SMR.

Although treatment with TNF- α antagonists has been associated with an increased risk of developing TB,⁴ there are other risk factors as well, including age, country of origin or current residence, international travel, history of exposure to people with TB, disease activity, and concomitant therapy with other immunomodulators. Two of the 5 new studies included in this analysis were conducted in China and Russia, where the incidence of TB is more than 6-fold higher than in the United States and Canada.³¹ Not unexpectedly, the majority of the new TB cases since 2009 were from the studies conducted in China and Russia; 2 new cases of active TB were reported from the study in China, and 4 of the 7 new cases of latent TB were reported from the study in Russia. The other 3 new cases of latent TB (United States, n=2; Canada, n=1) may reflect newer protocols requiring annual TB exposure rescreens, which may have contributed to the increased rate. All patients receiving adalimumab were screened for TB using chest x-ray, PPD skin test, and/or interferon-gamma release assays. Isolated cases of PPD conversion were observed during adalimumab treatment.

There was an increase in the rate of allergic reactions from the 2009 analysis (1.1 vs 3.9 E/100 PYs in 2009 vs 2015, respectively). The higher incidence of allergic reaction in the 2015 analysis likely resulted from a change in search methodology for terms of interest from searches using preferred terms and manual adjudication to searches automatically acquiring lower-level group MedDRA terms.. Of the 157 patients with allergic reactions in the 2015 data set, 32 had a medical history of atopic diathesis, asthma, hay fever, and/or atopic dermatitis including other drug allergies.

The incidence of opportunistic infections reported in 2015 decreased from 2009 (0.4 vs 0.02 E/100 PYs in 2009 vs 2015, respectively) likely because the rates from the 2015 but not the 2009 analysis excluded oral candidiasis.

Limitations of the current analysis include the lack of a long-term comparator group. Comparisons were limited to population databases for SIRs (SEER database, 2000–20007; NCI survey, 1977–1978) and SMRs (WHO mortality tables, 1997–2006). While patients with psoriasis may have received adalimumab in clinical practice for more than 10 years, maximum duration of adalimumab treatment in the current analysis was 5.5 years. Additionally, the clinical trial populations evaluated in this study may differ from the general clinical practice setting population because of the stringent inclusion/exclusion criteria inherent in clinical trials; hence, the interpretation of the data requires caution. Because there is limited information regarding the long-term safety of biosimilar drugs, a safety comparison between originator adalimumab and biosimilars is currently not feasible.

Nonetheless, this comprehensive long-term integrated analysis of adalimumab safety in 3727 patients with psoriasis enrolled in 18 clinical studies found no new safety signals and was comparable to the previous safety report. The AE rates remained stable and consistent with currently approved labelled indications over increased adalimumab exposure time.

Acknowledgments

The authors would like to acknowledge Winnie Lau and Kun Chen, of AbbVie Inc., for statistical analysis support. Medical writing support was provided by Janet Matsuura, PhD, Natalia Zhukovskaya, PhD, and Tiffany Brake, PhD, of Complete Publication Solutions, LLC (North Wales, PA, USA), and was funded by AbbVie Inc.

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Figure Legend

Figure 1. Duration of exposure to adalimumab for all patients. AAT=all adalimumab treatment set. Data from M14-193 were excluded (n=4).

Figure 2. Incidence rates with increasing adalimumab exposure: (a) serious adverse events, (b) serious infections, and (c) malignancies. AAT=all adalimumab treatment set. Data from M14-193 were excluded (n=4).

Figure 3. Standard incidence ratio analysis*. BCC=basal cell cancer; NCI=National Cancer Institute; NMSC=non-melanoma skin cancer; SCC=squamous cell cancer; SEER=Surveillance Epidemiology and End Results; SIR=standard incidence ratio. *Included in the analysis were clinical studies M02-528, M02-538, M03-656, M04-688, M04-716, M10-060, M10-238, M10-405, W10-151, M13-279, M13-606, M14-193, and W14-406 and related extension studies. Cancer rates from the NCI SEER program (2000–2007) and 1977–1978 NCI study (NMSC); in situ cancers are excluded from these rates. †Standardized mortality ratio.

Table 1. Baseline Demographics and Clinical Characteristics* in the All Adalimumab Treatment Set

Characteristic	November 2009 [†] (n=3010) ⁶	December 2015 (n=3723)
Age, y	44.7 (12.7)	44.7 (12.6)
Male, %	66.8	68.7
White, %	87.5	78.0
Geographic location, %		
Australia	0	0.6
Asia	5.4	15.7
Europe	30.1	26.5
North America	64.5	55.7
Russia	0	1.3
Duration of psoriasis, y	19.0 (11.7)	18.5 (11.7)
Body weight, kg	89.0 (22.0)	86.8 (21.9) [‡]
BSA affected, %	28.1 (18.7)	27.3 (18.7) [§]
PASI score	18.8 (8.5)	19.6 (9.6)
Patients with PsA, %	28.6 [¶]	26.5 [#]
BMI ≥30, kg/m ² (%)	42.3	37.6 ^{**}

AAT=all adalimumab treatment set; BMI=body mass index; BSA=body surface area;

PASI=Psoriasis Area and Severity Index; PsA=psoriatic arthritis.

Data from M14-193 were excluded (n=4).

*Values are expressed as mean (SD) unless indicated otherwise.

[†]In some cases, data were unavailable for up to 1% of patients.

[‡]Missing data, n=7.

[§]Missing data, n=437.

^{||}Missing data, n=38.

[¶]n=2034; history of PsA was not collected in M04-688.

[#]Missing data, n=163.

^{**}Missing data, n=36.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17084

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Table 2. Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ * of Patients in the All Adalimumab Treatment Set

	November 2009 n=3010	December 2015 n=3723
Exposure, PYs	4844.7	5429.0
Mean exposure per patient, mo	19.3	17.5
Adverse events, n (E/100 PYs)		
Nasopharyngitis	1182 (24.4)	1287 (23.7)
Upper respiratory tract infection	601 (12.4)	702 (12.9)
Headache	407 (8.4)	428 (7.9)
Arthralgia	262 (5.4)	282 (5.2)
Hypertension	233 (4.8)	246 (4.5)
Sinusitis	237 (4.9)	242 (4.5)
Cough	179 (3.7)	217 (4.0)
Back pain	194 (4.0)	208 (3.8)
Oropharyngeal pain	170 (3.5)	207 (3.8)

E/100 PY=events per 100 patient-years; PY=patient-year.

Data from M14-193 were excluded (n=4).

*Occurred in $\geq 5\%$ of patients in 2009; 2015 rates are shown for comparison.

Table 3. Adverse Events of Interest* in the All Adalimumab Treatment Set

	November 2009 n=3010	December 2015 n=3723
Exposure, PYs	4844.7	5429.0
Mean exposure per patient, mo	19.3	17.5
AEs, n (E/100 PYs)		
Any AE	15,177 (313.3)	16,536 (304.6)
Infectious AE	4301 (88.8)	4628 (85.2)
Serious AE	405 (8.4)	458 (8.4)
Serious infectious AE	80 (1.7)	99 (1.8)
Malignancy (excluding NMSC)	35 (0.7)	43 (0.8)
NMSC [†]	34 (0.7)	33 (0.6)
Melanoma [‡]	9 (0.2)	10 (0.2)
Lymphoma	1 (0.02)	1 (0.02)
Fatal AE	9 (0.2)	10 (0.2)
Opportunistic infections [§] (excluding TB)	20 (0.4)	1 (0.02)
TB	7 (0.1)	16 (0.3)
Active TB	7 (0.1)	9 (0.2)
Latent TB	0 (0)	7 (0.1)
Congestive heart failure	11 (0.2)	14 (0.3)
Allergic reaction	51 (1.1)	210 (3.9)
Demyelinating disease	1 (0.02)	1 (0.02)
Lupus-like reaction [†]	3 (0.16)	2 (0.04)

AE=adverse event; E/100PY=events per 100 patient-years; MedDRA=Medical Dictionary for Regulatory Activities; NMSC=non-melanoma skin cancer; PY=patient-year; TB=tuberculosis.

Data from M14-193 were excluded (n=4).

*For the 2015 data set, AE reports were queried automatically using lower-level MedDRA terms; in the 2009 data set, queries used MedDRA-defined preferred term group searches and company-defined preferred terms, requiring manual adjudication.

[†]Differences in some AE incidence rates between 2009 and 2015, including reduced rates, can be attributed to the updated clinical data, changes in the MedDRA version being used, or the application of new search strategies to identify all potential reports.

[‡]An event of lentigo maligna was not counted as a melanoma in the 2009 analysis but was counted in the 2015 analysis because of the difference in database querying. [§]Rates for 2009 included events of oral candidiasis, whereas rates from 2015 did not.

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10.1111/bjd.17084

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Table 4. Adverse Events of Interest* as of December 31, 2015; All Adalimumab Treatment Set

	n=3723
Exposure, PYs	5429.0
Mean exposure per patient, mo	17.5
AEs, n (E/100 PY)	
Injection-site reaction	595 (11.0)
Depression	79 (1.5)
Postoperative depression	1 (0.02)
Suicidal depression	1 (0.02)
Anxiety	64 (1.2)
Herpes zoster	44 (0.8)
Weight loss	13 (0.2)
Oral candidiasis	11 (0.2)
Ophthalmic herpes zoster	3 (0.06)
Inflammatory bowel disease	1 (0.02)
Suicide	1 (0.02)

AE=adverse event; E/100PY=events per 100 patient-years; MedDRA=Medical Dictionary for Regulatory Activities; PY=patient-year.

Data from M14-193 were excluded (n=4).

*For the 2015 data set, AE reports were queried automatically using lower-level MedDRA terms; in the 2009 data set, queries used MedDRA-defined preferred term group searches and company-defined preferred terms, requiring manual adjudication.