Long-Term Safety of Adalimumab in 29,967 Adult Patients From Global Clinical Trials Across Multiple Indications: An Updated Analysis

Gerd R. Burmester · Kenneth B. Gordon · James T. Rosenbaum ·

Dilek Arikan · Winnie L. Lau · Peigang Li · Freddy Faccin ·

Remo Panaccione

ABSTRACT

Introduction: The safety profile of adalimumab was previously reported in 23,458 patients across multiple indications. Here we report the long-term safety of adalimumab in adults with plaque psoriasis (Ps), hidradenitis suppurativa (HS), rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, non-radiographic axial spondyloarthritis, peripheral spondyloarthritis, Crohn's disease (CD), ulcerative colitis (UC), and non-infectious uveitis (UV).

Methods: Safety data from 77 clinical trials were pooled. Safety assessments included adverse events (AEs) and serious AEs (SAEs) that occurred after the first study dose and within 70 days (5 half-lives) after the last study dose.

Results: A total of 29,967 patients were included, representing 56,916 patient-years (PY) of exposure. The most frequently reported SAE of interest was infection (3.7/100 PY) with highest incidences in CD, RA, UV, and UC (3.5/100 PY–6.9/100 PY); serious infections in Ps (1.8/100 PY) and HS (2.8/100 PY) were lower. The observed number of deaths was below what would be expected in an age- and sex-adjusted population for most adalimumab-treated patients (including Ps). Lack of real-life data and limited long-term data (> 5 years) for most patients are limitations of this analysis.

Conclusion: The safety profile of adalimumab was consistent with previous findings and no new safety signals were observed.

Keywords: Adalimumab; Ankylosing spondylitis; Crohn's disease; Hidradenitis suppurativa; Long-term safety; Plaque psoriasis; Psoriatic arthritis; Rheumatoid arthritis; Ulcerative colitis; Uveitis

G. R. Burmester (✉)
Charité Universitätsmedizin Berlin, Berlin, Germany
e-mail: gerd.burmester@charite.de

K. B. Gordon
Medical College of Wisconsin, Milwaukee, WI, USA

J. T. Rosenbaum
Oregon Health and Science University and Legacy Devers Eye Institute, Portland, OR, USA

D. Arikan · W. L. Lau · P. Li · F. Faccin
AbbVie, North Chicago, IL, USA

R. Panaccione
University of Calgary, Calgary, AB, Canada

INTRODUCTION

Adalimumab (HUMIRA®, AbbVie, North Chicago, IL) is an anti-tumor necrosis factor (TNF) agent indicated for the treatment of 15 conditions, including adult and pediatric plaque psoriasis (Ps), hidradenitis suppurativa (HS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), polyarticular juvenile idiopathic arthritis (pJIA), enthesitis-related arthritis, adult and pediatric Crohn's disease (CD), ulcerative colitis (UC), adult and pediatric uveitis (UV), and Behçet's disease [1, 2].

The long-term safety of adalimumab was previously reported in 23,458 patients representing up to 12 years of clinical trial exposure [3]. Infections were the most frequently reported serious events, ranging from 1.4/100 patient-years (PY) to 6.7/100 PY across indications [3]. Non-melanoma skin cancer (NMSC) incidence rates were higher in Ps, RA, and CD compared with 10-year age-specific incidence rates in the USA from 1977 to 1978, but the overall malignancy rates (excluding NMSC) were as expected for the general population. Death rates were lower or equivalent to rates expected for the general population. The safety profile of adalimumab was also consistent with that of anti-TNF agents in real-world registries [4–7].

Since the previous analysis, adalimumab has been approved for new indications (e.g., HS and UV) and additional clinical trial data across indications have become available [1, 2]. The objective of this updated analysis was to examine the safety of adalimumab in adult patients with Ps, HS, RA, AS, nr-axSpA, peripheral SpA (pSpA), PsA, CD, UC, and UV, with a special focus on mortality rates with extended adalimumab treatment.

METHODS

Clinical Trials

Safety data from 77 clinical trials of adalimumab (33 RA [8–30], 13 Ps [31–44], 11 CD [45–57], 5 AS [58–62], 4 UC [63–67], 3 HS [68, 69], 3 PsA [70–73], 2 UV [74–76], 2 nr-axSpA [77, 78], 1 pSpA [79]) were included from randomized controlled, open-label, and long-term extension studies conducted through

December 31, 2016. Adalimumab postmarketing surveillance data were not included in this analysis because of limitations associated with voluntary reporting. Of note, this analysis did not include pediatric patients; a separate analysis on pediatric safety was recently published [80].

The studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki, and were approved by institutional review boards and/or independent ethics committees according to local law. All patients provided informed consent before any study procedures were conducted.

Safety Assessments

Safety assessments included all treatment-emergent adverse events (AEs) and serious AEs (SAEs) that occurred after the first adalimumab study dose and within 70 days (5 half-lives) after the last study dose. Events that were fatal or life threatening, required in-patient or prolonged hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly, required medical or surgical intervention to prevent a serious outcome, or other medically important conditions (e.g., miscarriage/spontaneous abortion, elective abortion) were categorized as SAEs. AEs were coded using the Medical Dictionary for Regulatory Activities version 19.1 preferred terms (https://www.meddra.org/). SAEs of interest included infections (including opportunistic infections and tuberculosis [TB]), demyelinating disorder, lupus-like syndrome, congestive heart failure (CHF), new onset or worsening of psoriasis, malignancy (including lymphoma, non-melanoma skin cancer [NMSC], and melanoma), and sarcoidosis. Rates are reported as events per 100 PY. Kaplan–Meier analyses were used to evaluate the time to first serious infection event and the time to first malignancy (excluding lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma).

Standardized incidence rates (SIRs) were calculated as the ratio of observed to expected number of malignancies; 95% CIs for SIRs were calculated assuming that observed malignancies

followed a Poisson distribution. To correspond with previously conducted SIR analyses of long-term adalimumab safety data, the data from the ReAlise uncontrolled observational study of patients with RA [23] were not included. The expected numbers of malignancies, 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, 2000–2007 (http://www.seer.cancer.gov). No similar database is available for Europe, Australia, or Canada, so an assumption was made that patients from these regions could be pooled with those from the USA. Because the NCI SEER database does not include NMSC, NMSC rates were based on age-specific incidence rates from an NCI survey in the USA from 1977 to 1978 [81].

Standardized mortality rates (SMR) were calculated as the ratio of observed deaths to expected deaths estimated on the basis of country-specific, baseline age- and sex-matched population data from the World Health Organization for 1997–2006 (https://www.who.int/gho/publications/world_health_statistics/whostat2006_erratareduce.pdf). The confidence interval of the SMR was calculated with a formula from Breslow and Day that uses Byar's approximation [82].

RESULTS

This analysis included 29,967 patients representing 56,916 PY of exposure. Baseline characteristics are summarized in Table 1. The highest adalimumab exposure was in the RA studies (37,106 PY), followed by Ps (5479 PY). Overall, 9355 patients had more than 2 years of exposure and 4003 patients had more than 5 years of exposure.

A total of 3867 (12.9%) patients discontinued because of a treatment-emergent AE (8.7/100 PY). The most common AEs leading to discontinuation in the total population were Crohn's disease (0.4/100 PY), rheumatoid arthritis (0.3/100 PY), ulcerative colitis (0.3/100 PY), and pneumonia (0.2/100 PY); all other events were reported with a rate of at most

Table 1 Baseline demographics and disease characteristics

Characteristic	RA	Ps	CD	UC	AS	HS	UV	PsA	nr-axSpA	pSpA	Total
N	15,512	3732	3896	1739	2026	733	464	837	863	165	29,967
Age, mean, years	53.5	44.7	37.0	41.0	40.9	36.5	42.9	48.4	37.4	40.6	47.4
Disease duration,[a] mean, years	9.3	18.8	10.3	8.0	9.6	11.6	4.5	14.6	2.1	3.6	10.4
Female, %	78.7	31.3	59.2	39.4	26.0	66.6	58.2	47.4	51.6	54.5	62.0
Concomitant DMARDs, %	71.3	3.9	58.1	71.4	33.7	14.7	47.6	64.4	21.1	49.1	55.2
Concomitant systemic steroids, %	63.9	5.1	48.4	66.3	17.9	27.8	65.5	29.9	19.9	38.8	48.4
From US sites, %	24.5	30.9	34.8	17.7	7.2	46.4	28.4	25.3	13.4	11.5	25.3
Exposure, PY	37,106	5479	4359	3407	2120	1198	1151	998	709	391	56,916
Duration of exposure											
Median, years	1.0	0.5	0.5	0.8	0.4	1.1	2.4	0.4	0.5	2.8	0.7
Maximum, years	12.1	5.7	5.5	8.4	5.1	4.2	6.1	3.5	3.0	3.1	12.1
> 2 years of exposure, n (%)	5304 (34.2)	1244 (33.3)	704 (18.1)	620 (35.7)	360 (17.8)	287 (39.2)	278 (59.9)	312 (37.3)	124 (14.4)	122 (73.9)	9355 (31.2)
> 5 years of exposure, n (%)	3494 (22.5)	86 (2.3)	35 (0.9)	217 (12.5)	140 (6.9)	0	31 (6.7)	0	0	0	4003 (13.4)

AS ankylosing spondylitis, *CD* Crohn's disease, *DMARD* disease-modifying antirheumatic drug, *HS* hidradenitis suppurativa, *nr-axSpA* non-radiographic axial SpA, *Ps* plaque psoriasis, *PsA* psoriatic arthritis, *pSpA* peripheral SpA, *PY* patient-year, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *UC* ulcerative colitis, *UV* uveitis
[a] Data missing for 176 patients, including 155 patients with RA, 18 patients with PsA, 1 patient with CD, and 2 patients with UC

Table 2 Incidence rates of serious adverse events of interest

SAE[a]	RA	Ps	CD	UC	AS	HS	UV	PsA	nr-axSpA	pSpA	Total
N	15,512	3732	3896	1739	2026	733	464	837	863	165	29,967
Exposure, PY	37,106	5479	4359	3407	2120	1198	1151	998	709	391	56,916
Infection	3.9	1.8	6.9	3.5	1.8	2.8	4.1	2.8	2.5	1.0	3.7
Tuberculosis	0.2	0.2	0.2	< 0.1	0.1	0	0.4	0.2	0.1	0.3	0.2
Active	0.2	0.2	0.1	< 0.1	0.1	0	0.2	0.2	0.1	0	0.2
Latent	< 0.1	0	< 0.1	0	0	0	0.3	0	0	0.3	< 0.1
Opportunistic infection[b]	< 0.1	0	< 0.1	< 0.1	0	0	0.4	0	0.1	0	< 0.1
Demyelinating disorder[c]	< 0.1	0	0.1	< 0.1	< 0.1	0	0.3	0	0	0	< 0.1
Lupus-like syndrome	< 0.1	0	< 0.1	< 0.1	< 0.1	0	< 0.1	0	0.1	0	< 0.1
CHF[d]	0.2	0.1	0	< 0.1	< 0.1	0.2	< 0.1	0	0	0	0.2
Ps[e]	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0	0.1	0	0	< 0.1
Malignancy[f]	0.7	0.5	0.4	0.6	0.2	0.5	0.7	0.2	0.1	0.3	0.6
Lymphoma	0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.2	0	0	< 0.1
NMSC	0.2	0.1	< 0.1	< 0.1	0.2	< 0.1	0.2	0.1	0	0	0.1
Melanoma	< 0.1	0.2	0	< 0.1	< 0.1	0	0	0	0	0	< 0.1
Sarcoidosis	< 0.1	0	0	0	< 0.1	0	< 0.1	0	0	0	< 0.1
Any AE leading to death	0.6	0.2	0.1	0.1	< 0.1	0.5	0.6	0.3	0.3	1.0	0.5

AE adverse event, *AS* ankylosing spondylitis, *CD* Crohn's disease, *CHF* congestive heart failure, *HS* hidradenitis suppurativa, *NMSC* non-melanoma skin cancer, *nr-axSpA* non-radiographic axial SpA, *Ps* plaque psoriasis, *PsA* psoriatic arthritis, *pSpA* peripheral SpA, *PY* patient-year, *RA* rheumatoid arthritis, *SAE* serious adverse event, *SpA* spondyloarthritis, *UC* ulcerative colitis, *UV* uveitis

[a] Reported in events/100 PY
[b] Excludes oral candidiasis and tuberculosis
[c] Includes multiple sclerosis (8 events), demyelination (7 events), optic neuritis (6 events), Guillain–Barré syndrome (3 events), and leukoencephalopathy (1 event)
[d] Includes cardiac failure congestive (44 events), cardiac failure (34 events), right ventricular failure (5 events), cardiogenic shock (3 events), cardiac failure acute (3 events), pulmonary edema (3 events), left ventricular dysfunction (2 events), left ventricular failure (2 events), and acute left ventricular failure (1 event)
[e] New onset or worsening
[f] Excludes lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma

0.1/100 PY. Most of these observed discontinuations can be attributed to the underlying disease or its complications.

Serious infections were the most frequent SAEs of interest across all indications (3.7/100 PY), with the highest incidences in CD, UV, RA, and UC studies (3.5–6.9/100 PY); rates in pSpA (1.0/100 PY), Ps (1.8/100 PY), and AS (1.8/100 PY) were lower (Table 2). Overall, the most commonly reported serious infections were pneumonia (0.6/100 PY) and cellulitis (0.2/100 PY). The most common serious infections in RA, Ps, and HS were pneumonia (0.7/100 PY, 0.3/100 PY, and 0.3/100 PY), cellulitis (0.2/100 PY, 0.3/100 PY, and 0.3/100 PY), arthritis bacterial (0.2/100 PY, RA only), and pilonidal

cyst (0.3/100 PY, HS only). For other indications, the most common serious infections were cellulitis (0.6/100 PY) and appendicitis (0.3/100 PY) in nr-axSpA; urinary tract infection (0.5/100 PY) and pneumonia (0.4/100 PY) in UV; urinary tract infection (0.4/100 PY), appendicitis (0.2/100 PY), and diverticulitis (0.2/100 PY) in PsA; anal (1.0/100 PY) and abdominal (0.7/100 PY) abscess in CD; and pneumonia (0.5/100 PY) and appendicitis (0.3/100 PY) in UC. In pSpA studies, four serious infections were reported (cellulitis, diverticulitis, pyelonephritis, and hemorrhagic cystitis; 0.3/100 PY each). In AS, cellulitis (0.2/100 PY)
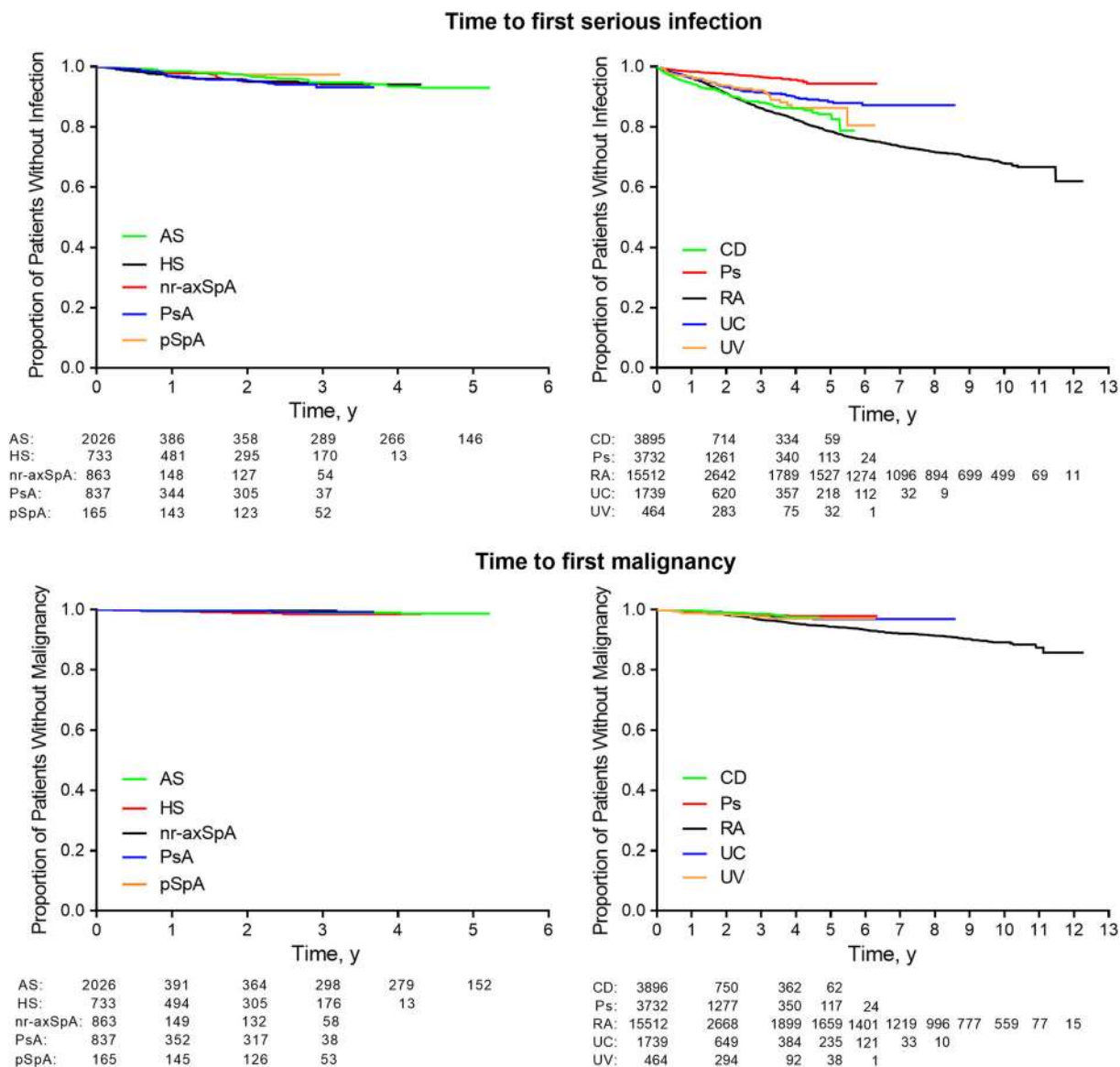
Fig. 1 Time to first serious infection by indication and time to first malignancy, other than lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma by indication. Numbers of patients assessed at each time point for each indication are shown below each graph. *AS* ankylosing spondylitis, *CD* Crohn's disease, *HS* hidradenitis suppurativa, *nr-axSpA* non-radiographic axial SpA, *Ps* plaque psoriasis, *PsA* psoriatic arthritis, *pSpA* peripheral SpA, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *UC* ulcerative colitis, *UV* uveitis

was the most common serious infection event; no other event exceeded 0.2/100 PY. Risk of serious infection event was generally stable across time for all indications (Fig. 1).

The overall rate of serious TB was 0.2/100 PY (Table 2). The highest rate of serious active TB was observed among patients with Ps, RA, PsA, and UV. No cases of active TB were seen in patients with HS or pSpA, and no cases of latent TB were seen among patients with Ps, HS, AS, nr-axSpA, PsA, or UC; however, testing for latent TB was not performed in most trials after treatment was started.

The overall rate of serious opportunistic infections, excluding TB and oral candidiasis, was less than 0.1/100 PY (27 events), with the highest rate reported in UV studies (0.4/100 PY; 5 events); the rate of opportunistic infections did not exceed 0.1/100 PY in other indications (Table 2). The most common serious opportunistic infection was esophageal candidiasis (< 0.1/100 PY; 4 events); no other event occurred more than twice. No serious opportunistic infections were reported in Ps, HS, AS, pSpA, and PsA studies (Table 2), and no events of serious oral candidiasis were reported in any of the studies. The rates of serious demyelinating disorders, lupus-like syndrome, and new onset/worsening of psoriasis and sarcoidosis across all indications were at most 0.1/100 PY. With the exception of UV (0.3/100 PY; 3 events), the rate of demyelinating disorders did not exceed 0.1/100 PY across individual indications (25 events across all indications; Table 2). The overall rate of serious CHF was 0.2/100 PY (97 events), with the highest rate (0.2/100 PY) occurring in patients with HS and RA (Table 2). No cases of progressive multifocal leukoencephalopathy were reported in these adalimumab clinical trials.

The overall rate of serious malignancies, excluding serious lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma, was 0.6/100 PY across indications (ranging from 0.1 to 0.7/100 PY), with the highest rates reported among RA, UV, and UC studies (Table 2). The time to first malignancy, excluding lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma, was similar between indications (Fig. 1). The SIR for

all malignancies (excluding NMSC) was based on 321 observed events and was similar to the age-specific incidence rates (Fig. 2). The observed numbers of malignancies for most individual adalimumab populations (RA, Ps, AS, nr-axSpA, pSpA, and PsA) were below the age-specific rates. The SIR for lymphomas was based on 44 events (with 33 events in the RA population); the number of lymphomas observed across indications and in the RA studies were significantly greater than expected for age-specific incidence rates (Fig. 2). The SIR for NMSC was based on 280 events (with 191 basal cell carcinoma, 79 squamous cell carcinoma, and 10 unclassified), and the number of events across indications and in the RA, Ps, and CD studies was significantly greater than expected for age-specific incidence rates (Fig. 2). Although the SIR for NMSC was higher for HS and UV compared with Ps, RA, and CD, it was not significantly different from expected age-specific incidence rates in these two populations. The SIR for melanomas was based on 24 events (RA, 14 events; Ps, 6 events; UC, 3 events; AS, 1 event). In patients with Ps, the SIR for melanoma was significantly higher compared with age-specific incidence rate.

Overall, 232 deaths were recorded. Deaths were reported in each indication, with the highest rates among RA and UV studies (0.6/100 PY). For most of the adalimumab populations (Ps, RA, AS, PsA, UC, and CD), the observed number of deaths was below what would be expected in an age- and sex-adjusted general population (Fig. 3). For HS, nr-axSpA, pSpA, and UV studies, the small size of these trials precluded accurate assessment of the standardized mortality ratio, and the 95% CIs all included 1.0.

DISCUSSION

This analysis of 29,967 adult patients, representing 10 indications and 56,916 PY of adalimumab exposure, is the most comprehensive safety analysis of adalimumab clinical trials reported to date. These results add to the previous safety analyses [3, 83] and the pediatric safety analysis [80] and demonstrate that no
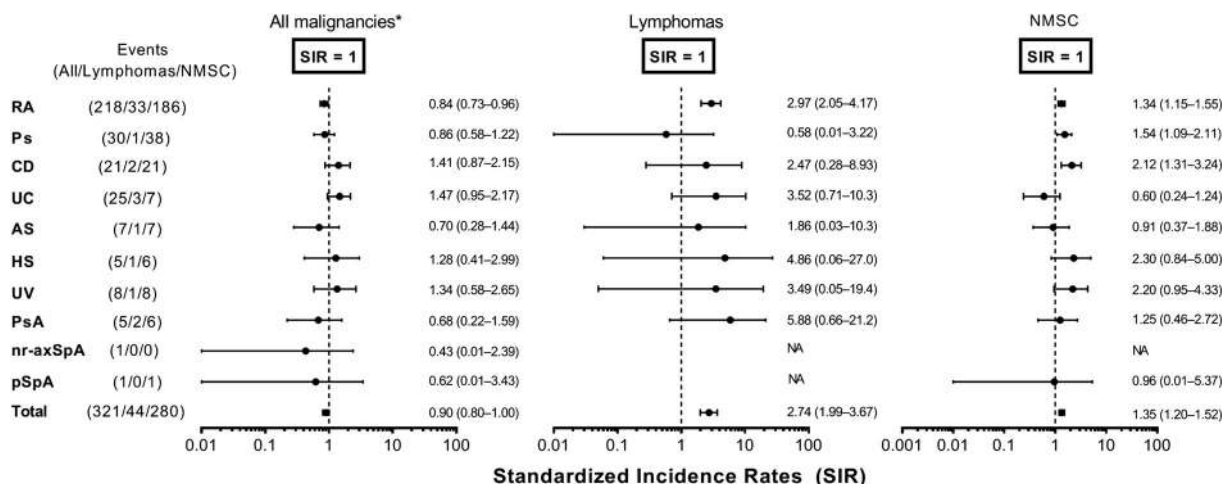
Fig. 2 Standardized incidence rates (95% CI) of all malignancies (excluding NMSC), lymphomas, and NMSC for all indications and individual populations. SIR values less than 1 indicate fewer events were observed than expected. *All malignancies, excluding NMSC. Total population comprised 29,986 patients, including an additional 20 patients with Behçet's disease; data were missing for 1 patient with RA. *AS* ankylosing spondylitis, *CD* Crohn's disease, *HS* hidradenitis suppurativa, *NMSC* non-melanoma skin cancer, *nr-axSpA* non-radiographic axial SpA, *Ps* plaque psoriasis, *PsA* psoriatic arthritis, *pSpA* peripheral SpA, *RA* rheumatoid arthritis, *SIR* standardized incidence rate, *SpA* spondyloarthritis, *UC* ulcerative colitis, *UV* uveitis
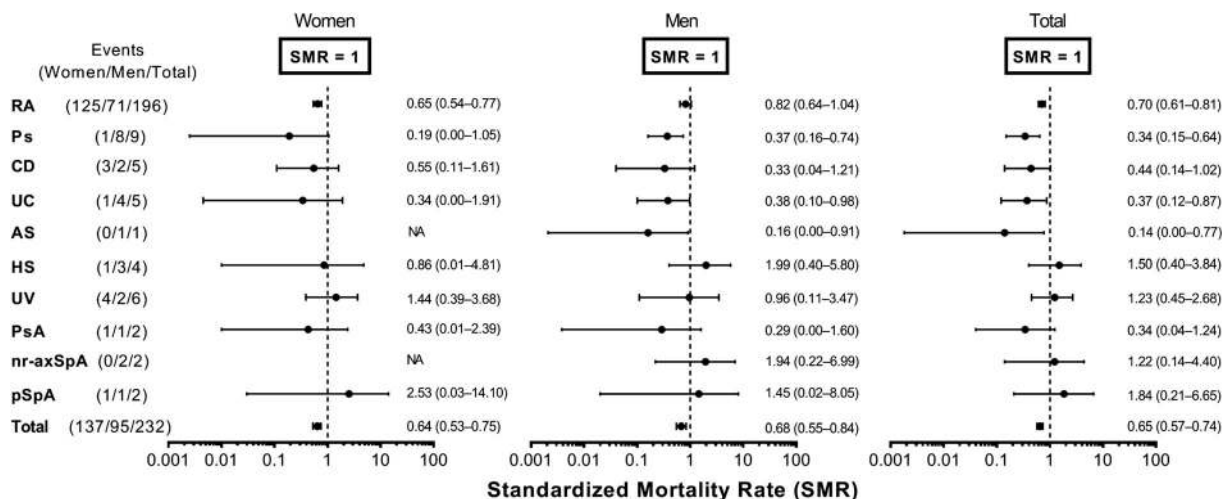
Fig. 3 Standardized mortality rates (95% CI) for all indications and individual populations. Total population comprised 29,986 patients, including an additional 20 patients with Behçet's disease; data were missing for 1 patient with RA. *AS* ankylosing spondylitis, *CD* Crohn's disease, *HS* hidradenitis suppurativa, *nr-axSpA* non-radiographic axial SpA, *Ps* plaque psoriasis, *PsA* psoriatic arthritis, *pSpA* peripheral SpA, *RA* rheumatoid arthritis, *SMR* standardized mortality rate, *SpA* spondyloarthritis, *UC* ulcerative colitis, *UV* uveitis

new safety findings were noted with increasing adalimumab exposure. Rates of SAEs of interest remained low and consistent with those reported for TNF inhibitors [4–7].

Infections remained the most commonly reported SAE across indications [3]. The overall rate of serious infections was 3.7/100 PY and ranged from 1.0 to 6.9/100 PY across

indications, with the highest rates reported among patients with CD, UV, RA, and UC and lowest among patients with pSpA, psoriasis, and AS. These are similar to serious infection rates reported for adalimumab in real-world registries [84–86] as well as for those reported for other TNF inhibitors [5–7, 84, 87, 88]. The higher rates of infections among patients with CD, RA, UV, and UC may be associated with concomitant corticosteroid use, which was highest among these patient populations, and patient characteristics, such as age and disease duration [6, 7, 89, 90]. For example, for CD and UC, an increased rate of infection may occur early in the course of treatment, while in severe disease, infection may be related to the underlying disease, independent of treatment.

Opportunistic infections are possible with TNF inhibitor therapy as a result of their immunosuppressive nature [91]. Our long-term analysis demonstrated that the overall rates of serious opportunistic infections (excluding tuberculosis and oral candidiasis) and serious active tuberculosis were low. With the exception of UV, the rates of serious opportunistic infections were at most 0.1/100 PY across indications. The highest rate of serious active TB was found among patients with Ps, RA, PsA, and UV. The rates of serious opportunistic infections and active TBs were similar to the previous analysis [3] and were consistent with rates reported for adalimumab and other TNF inhibitors in clinical and real-world registry studies [86, 92–96].

The rates of other SAEs of interest were low. The overall rates of serious demyelinating disorders, lupus-like syndrome, and sarcoidosis were less than 0.1/100 PY. The overall rate of serious CHF was 0.2/100 PY, with the highest rates observed in HS and RA. This is noteworthy considering that patients with Ps have increased incidence and prevalence of cardiovascular risk factors [97]. However, the risk of cardiovascular events was also low with TNF inhibitor therapy in real-world registries of Ps [4, 86] and RA [5, 98]. Furthermore, recent studies have suggested decreased risk of cardiovascular events with TNF inhibitor therapy in patients with Ps, RA, and PsA [99, 100]. Future studies are needed to confirm these results.

The SIR for all malignancies (excluding NMSC) was similar to the age-specific incidence rates and the observed numbers of malignancies for most individual adalimumab populations (RA, Ps, AS, PsA, nr-axSpA, and pSpA) were below the age-specific rates. Overall, the rate of serious malignancies was generally similar to that reported for TNF inhibitors in real-world Ps and RA registries [4, 101–103]. The time to onset of a first malignant event was stable across indications, suggesting no increased risk over time with prolonged treatment. However, the SIRs for lymphoma and NMSC in patients with RA were higher than those observed in age-matched populations. In addition, increased incidences of NMSC were observed in patients with Ps and CD compared with age-matched populations. These findings were not entirely unexpected because increased risk of lymphoma and/or NMSC has been reported in patients with Ps, RA, and CD [104–108]. Furthermore, elevated rates of lymphoma and NMSC have been reported in patients with CD and RA receiving TNF inhibitors [103, 105, 109, 110]. However, TNF inhibitor treatment did not significantly increase the risk of lymphoma or NMSC in two other studies in patients with RA [108, 111]. Similar observations were reported in a Swedish registry analysis among patients with AS and PsA [112].

The risk of mortality was not increased in adalimumab-treated patients compared with the general population, and for most patients (including Ps) the observed number of deaths was below what would be expected in an age- and sex-adjusted population. There are a few possibilities to explain these interesting findings. First, the so-called healthy-cohort effect resulting from tighter monitoring and possible lifestyle changes (less smoking, healthier diet, more exercise) of patients in clinical trials may affect mortality. Second, the reduction in inflammation observed with anti-cytokine treatment may lead to fewer cardiovascular events and thus lowered mortality rate [113, 114], and decreased risk of cardiovascular events with TNF inhibitor therapy reported in patients with Ps, RA, and PsA [99, 100]. However, it may also be possible that the improved life expectancy results from the rigorous

screening (and exclusion criteria) before entering the trial and then the careful medical care that follows.

Limitations of this analysis of randomized clinical studies included the lack of real-life data and limited long-term data (> 5 years) for most patients. Nevertheless, this is a comprehensive long-term safety analysis of adalimumab studies that included 9355 patients with more than 2 years of exposure (compared with 5209 patients in the previous analysis) and 4003 patients with more than 5 years of exposure (compared with 1971 patients in the previous analysis) [3]. Other strengths of this analysis included rigorous safety monitoring in the clinical trials, reporting for several indications, and robust mortality data.

CONCLUSIONS

Taken together, this analysis of adalimumab trials with 56,916 PY of exposure demonstrated an overall safety profile consistent with previous findings [3, 83, 115, 116] and with other anti-TNF agents [4–7]. No new safety signals or tolerability issues were identified, and the risk of mortality was not increased compared with the general population.

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Compliance with Ethics Guidelines. The individual studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki, and were approved by institutional review boards and/or independent ethics committees according to local law. All patients provided informed consent before any study procedures were conducted.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. Access is provided to anonymized, patient- and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports) from AbbVie-sponsored phase II–IV global interventional clinical trials conducted in patients (completed as of May 2004, for products and indications approved in either the USA or the European Union), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. Access to this clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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