Long-Term Safety of Adalimumab (HUMIRA) in Adult Patients From Global Clinical Trials Across Multiple Indications: an Updated Analysis in 29 987 Patients Representing 56 951 Patient-Years

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BACKGROUND

- Adalimumab is an anti–tumor necrosis factor-α (TNF-α) agent indicated for the treatment of immune-mediated diseases[1,2]
- Serious adverse events (AEs) of interest with anti–TNF-α agents include serious infections and malignancy[3,4]
- The long-term safety of adalimumab has been previously reported in 23 458 patients representing up to 12 years of clinical trial exposure (through November 2010) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (Ps), and Crohn's disease (CD)[5]
- In the previous analysis[5]
  - Infections were the most frequently reported serious events across indications
  - Non-melanoma skin cancer (NMSC) incidence was raised in RA, Ps, and CD compared with 10-year age-specific incidence rates in the United States from 1977 to 1978, but the overall malignancy rates were as expected for the general population
  - Death rates were not increased compared with rates expected for the general population

OBJECTIVE

- To report an updated analysis examining the long-term safety of adalimumab in adult patients with RA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), peripheral SpA (pSpA), PsA, Ps, hidradenitis suppurativa (HS), CD, ulcerative colitis (UC), and non-infectious uveitis (UV)

METHODS

- Safety data from 78 clinical trials of adalimumab were included in these analyses
  - Number of included trials per indication: RA, 33; AS, 5; nr-axSpA, 2; pSpA, 1; PsA, 3; Ps, 13; HS, 3; CD, 11; UC, 4; UV, 2; other, 1
- Trials were randomized, controlled, open-label, and long-term extension studies conducted in Europe, North America, South America, Asia, Australia, New Zealand, and South Africa through December 31, 2016
- Adalimumab postmarketing surveillance data were not included in this analysis
- Safety assessments included all AEs and serious AEs (SAEs) that occurred after the first adalimumab study dose and up to 70 days (5 half-lives) after the last study dose
  - SAEs were defined as events that were fatal or immediately life-threatening, required in-patient hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly, or required medical or surgical intervention to prevent a serious outcome
  - SAEs of interest included infections (eg, opportunistic infections, tuberculosis), demyelinating disorder, lupus-like syndrome, congestive heart failure, new onset or worsening of psoriasis, malignancy (eg, lymphoma, NMSC, melanoma), and sarcoidosis.
  - Rates are reported as events per 100 patient-years (PYs); Kaplan-Meier analyses were used to evaluate the time to first serious infection and time to first malignancy/lymphoma/NMSC for each indication
- Standardized mortality rates were calculated as the ratio of observed deaths to expected deaths estimated based on country-specific and age- and sex-matched population data from the World Health Organization for 1997–2006[6]
  - The 95% confidence intervals for the standardized mortality rates were calculated using Byar's approximation

RESULTS

- This analysis included 29 987 patients representing 56 951 PYs of exposure **(Table 1)**
- Most of the adalimumab exposure was in RA studies, at 37 106 PYs
- Demographic and baseline characteristics of the analysis population are shown in **Table 1**

Table 1. Demographic and Baseline Disease Characteristics*

Characteristic	RA	AS	nr-axSpA	pSpA	PsA	Ps	HS	CD	UC	UV	Total†
N	15512	2026	863	165	837	3732	733	3896	1739	464	29987
Mean age, y	53.5	40.9	37.4	40.6	48.4	44.7	36.5	37.0	41.0	42.9	47.4
Mean disease duration, y	9.3	9.6	2.1	3.6	14.6	18.8	11.6	10.3	8.0	4.5	10.4
Female, %	78.7	26.0	51.6	54.5	47.4	31.3	66.6	59.2	39.4	58.2	62.0
Receiving concomitant DMARDs, %	71.3	33.7	21.1	49.1	64.4	3.9	14.7	58.1	71.4	47.6	55.2
Receiving concomitant systemic corticosteroids, %	63.9	17.9	19.9	38.8	29.9	5.1	27.8	48.4	66.3	65.5	48.4
From US sites, %	24.5	7.2	13.4	11.5	25.3	30.9	46.4	34.8	17.7	28.4	25.3
Exposure, PYs	37106	2120	709	391	998	5479	1198	4359	3407	1151	56951
Median duration of exposure, y	1.0	0.4	0.5	2.8	0.4	0.5	1.1	0.5	0.8	2.4	0.7
Maximum duration of exposure, y	12.1	5.1	3.0	3.1	3.5	5.7	4.2	5.5	8.4	6.1	12.1
>2 years of exposure, n (%)	5304 (34.2)	360 (17.8)	124 (14.4)	122 (73.9)	312 (37.3)	1244 (33.3)	287 (39.2)	704 (18.1)	620 (35.7)	278 (59.9)	9363 (31.2)
>5 years of exposure, n (%)	3494 (22.5)	140 (6.9)	0	0	0	86 (2.3)	0	35 (0.9)	217 (12.5)	31 (6.7)	4003 (13.3)

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.
*Data are from 78 clinical trials and their long-term extensions studies.
†Total includes the 10 populations shown plus 20 patients with Behcet's disease (35.5 PYs).

SERIOUS AEs

Serious Infections

- The most frequently reported SAE of interest was infection (highest incidences in CD, RA, UV, and UC; **Table 2**); the most commonly reported serious infections were pneumonia (0.6/100 PY) and cellulitis (0.2/100 PY)

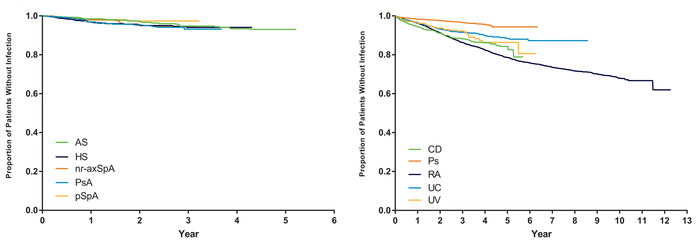
Table 2. Incidence Rates of Serious AEs of Interest

AEs of Interest*	RA	AS	nr-axSpA	pSpA	PsA	Ps	HS	CD	UC	UV	Total†
N	15512	2026	863	165	837	3732	733	3896	1739	464	29987
Exposure, PYs	37106	2120	709	391	998	5479	1198	4359	3407	1151	56951
Serious infection	3.9	1.8	2.5	1.0	2.8	1.8	2.8	6.9	3.5	4.1	3.7
Tuberculosis	0.2	0.1	0.1	0.3	0.2	0.2	0	0.2	<0.1	0.4	0.2
Active	0.2	0.1	0.1	0	0.2	0.2	0	0.1	<0.1	0.2	0.2
Latent	<0.1	0	0	0.3	0	0	0	<0.1	0	0.3	<0.1
Opportunistic infection‡	<0.1	0	0.1	0	0	0	0	<0.1	<0.1	0.4	<0.1
Demyelinating disorder	<0.1	<0.1	0	0	0	0	0	0.1	<0.1	0.3	<0.1
Lupus-like syndrome	<0.1	<0.1	0.1	0	0	0	0	<0.1	<0.1	<0.1	<0.1
CHF	0.2	<0.1	0	0	0	0.1	0.2	0	<0.1	<0.1	0.2
Ps new onset/worsening	<0.1	<0.1	0	0	0.1	<0.1	<0.1	<0.1	<0.1	0	<0.1
Malignancy§	0.7	0.2	0.1	0.3	0.2	0.5	0.5	0.4	0.6	0.7	0.6
Lymphoma	0.1	<0.1	0	0	0.2	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
NMSC	0.2	0.2	0	0	0.1	0.1	<0.1	<0.1	<0.1	0.2	0.1
Melanoma	<0.1	<0.1	0	0	0	0.2	0	0	<0.1	0	<0.1
Sarcoidosis	<0.1	<0.1	0	0	0	0	0	0	0	<0.1	<0.1
Any AE leading to death	0.6	<0.1	0.3	1.0	0.3	0.2	0.5	0.1	0.1	0.6	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; SpA, spondyloarthritis; UC, ulcerative colitis; UV, uveitis.
Data from 78 clinical trials and their long-term extensions studies.
*Reported in events/100 PYs.
†Total includes the 10 populations shown plus 20 patients with Behcet's disease (35.5 PYs).
‡Excludes oral candidiasis and tuberculosis.
§Excludes lymphoma, hepatosplenic T-cell lymphoma, leukemia, NMSC, and melanoma.

- Risk of serious infectious event was generally stable across time for all indications **(Figure 1)**

Figure 1. Time to First Serious Infection by Indication

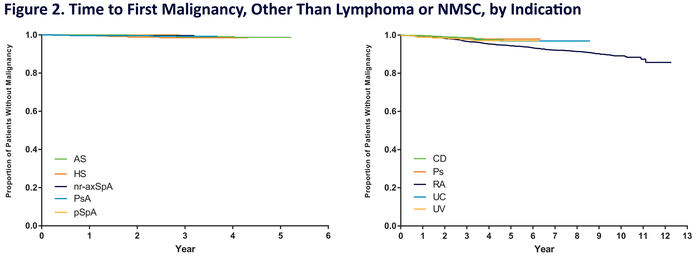


AS, ankylosing spondylitis; CD, Crohn's disease; HS, hidradenitis suppurativa; nr-axSpA, non-radiographic axial SpA; Ps, plaque psoriasis; PsA, psoriatic arthritis; pSpA, peripheral SpA; RA, rheumatoid arthritis; SpA, spondyloarthritis; UC, ulcerative colitis; UV, uveitis.

MALIGNANCIES

- The overall rate of serious malignancies, excluding lymphoma, NMSC, and melanoma, was 0.6/100 PY (ranging from 0.1 to 0.7/100 PY across indications), with the highest rates reported among RA, UV, and UC studies **(Table 2)**
  - The overall rate of NMSC was (0.1/100 PY), ranging from 0 to 0.2/100 PY across indications
- The time to first malignancy, excluding lymphoma and NMSC, did not show marked differences between indications **(Figure 2)**

Figure 2. Time to First Malignancy, Other Than Lymphoma or NMSC, by Indication

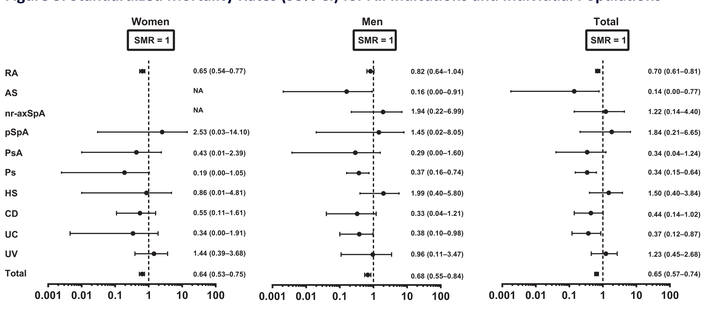


AS, ankylosing spondylitis; CD, Crohn's disease; HS, hidradenitis suppurativa; nr-axSpA, non-radiographic axial SpA; Ps, plaque psoriasis; PsA, psoriatic arthritis; pSpA, peripheral SpA; RA, rheumatoid arthritis; SpA, spondyloarthritis; UC, ulcerative colitis; UV, uveitis.

MORTALITY RATES COMPARED WITH DATA FROM THE GENERAL POPULATION

- Overall and for most of the adalimumab populations (AS, PsA, Ps, UC, CD, and RA), the observed number of deaths was below what would be expected in an age- and sex-adjusted population **(Figure 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

Figure 3. Standardized Mortality Rates (95% CI) for All Indications and Individual Populations



AS, ankylosing spondylitis; CD, Crohn's disease; HS, hidradenitis suppurativa; NA, not available; 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.

CONCLUSIONS

- This analysis of data from clinical trials of adalimumab demonstrated an overall safety profile consistent with previous findings[5,7–9] and with the TNF-α inhibitor class[10]
- No new safety signals or tolerability issues with adalimumab treatment were identified
- For most indications, the mortality rate was below what would be expected in an age- and sex-adjusted population
- Efficacy and safety data continue to support the well-established benefits of adalimumab for the approved indications

DISCLOSURES

GR Burmester has received research grants, consulting fees, and speaker fees from AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Roche, and UCB.

R Panaccione has served as a consultant to Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Centocor, Elan, Ferring, GlaxoSmithKline, Procter and Gamble, Schering-Plough, Shire, and UCB; received grants from Abbott Laboratories, Axcan, Bristol-Myers Squibb, Centocor, Elan, Millennium, and Procter and Gamble; and received honoraria from Abbott Laboratories, AstraZeneca, Byk Solvay, Centocor, Elan, Janssen, Procter and Gamble, Prometheus, Schering-Plough, and Shire.

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D Arikan, WL Lau, and R Tarzynski-Potempa are full-time employees of AbbVie and may own AbbVie stock and/or stock options.

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