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CONCISE REPORT

Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis

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ABSTRACT

Background Adalimumab has been used in patients with moderately to severely active rheumatoid arthritis (RA) for over 10 years and has a well-established safety profile across multiple indications.

Objective To update adverse events (AEs) of special interest from global adalimumab clinical trials in patients with RA.

Methods This analysis includes 15 132 patients exposed to adalimumab in global RA clinical trials. AEs of interest included overall infections, laboratory abnormalities and AEs associated with influenza vaccination. Pregnancy outcome data were collected from the Adalimumab Pregnancy Registry.

Results Serious infections and tuberculosis occurred at a rate of 4.7 and 0.3 events/100 patient-years, respectively. Two patients experienced hepatitis B reactivation. No significant laboratory abnormalities were reported with adalimumab-plus-methotrexate compared with placebo-plus-methotrexate. Influenza-related AEs occurred in 5% of vaccinated patients compared with 14% of patients not vaccinated during the study. Relative risk of major birth defects and spontaneous abortions in adalimumab-exposed women were similar between that of unexposed women with RA and healthy women.

Conclusions This analysis confirms and expands the known safety profile of adalimumab and reports no additional safety risk of laboratory abnormalities, hepatitis B reactivation and pregnancy outcomes, including spontaneous abortions and birth defects. The benefits of influenza vaccination are reinforced.

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INTRODUCTION

Tumour necrosis factor inhibitors (anti-TNFs) have contributed to improved clinical outcomes in rheumatoid arthritis (RA), but safety has been one point of relative concern. Serious infectious event (SIE) rates are increased in patients using biologics, and risk minimisation activities, such as vaccinations and latent tuberculosis (TB) infection (LTBI) screening and prophylaxis can mitigate infection risk.^{1 2} Recently, other adverse events (AEs) have

become a focus of interest: viral reactivation, vaccination response, laboratory abnormalities and pregnancy outcomes.

This analysis focuses on these emerging events, using comprehensive data from global adalimumab clinical trials in RA.

PATIENTS AND METHODS**Data sources**

AE data were derived from 28 global clinical trials (see online supplementary table S1) with adalimumab in patients with RA. The Adalimumab Pregnancy Exposure Registry (APER) is an ongoing prospective, observational, exposure cohort study conducted in North America to monitor pregnancy outcome in women with RA exposed to adalimumab during pregnancy compared with a disease-matched group of women with RA who have not used adalimumab during pregnancy and a cohort of healthy pregnant women. This cohort study is being conducted by the Organization of Teratology Information Specialists (OTIS).³ Data reported are collected from 1 February 2004 through 5 November 2013.

Safety assessments and statistical analyses

The safety population consists of all study patients with any adalimumab use from the first dose through 70 days (five half-lives) after the last study dose. Serious AE (SAE) was defined as fatal or immediately life-threatening; required hospitalisation or prolonged hospitalisation; resulted in persistent or significant disability/incapacity, congenital anomaly or required medical or surgical intervention to prevent a serious outcome. AEs were summarised as events/100 patient-years (E/100 PY) of adalimumab exposure, using preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) V15.1 (<http://www.meddra.org>).

AEs of interest included overall SIEs, TB, opportunistic infections, herpes zoster (HZ) and hepatitis B reactivation.

Percentages of patients who developed anaemia during the first 6 months of adalimumab treatment were determined in two studies in patients with early (<1 year),^{4 5} and one with long-standing RA (>1 year).⁶ Mean change from baseline in fasting serum lipid concentrations (total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)) and haemoglobin (Hb) were compared between adalimumab-plus-methotrexate



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(MTX) and placebo-plus-MTX (MTX-monotherapy) at week 26 in the OPTIMA study,⁵ using a contrast within a one-way analysis of variance.

Influenza-related AEs rates following influenza vaccination were assessed in adalimumab-treated patients with RA for 10 years.⁷ AEs related to influenza virus infection (within 270 days of vaccination) were tabulated using a predefined MedDRA Query.

All pregnancies enrolled in the OTIS pregnancy registry that reached a pregnancy outcome by November 2013 were included. Pregnancy outcomes included live births, major and minor birth defects, spontaneous abortions, preterm delivery (<37 weeks) and mean gestational age at delivery. Pregnancies exposed to MTX were excluded, due to known teratogenicity.⁸ Maternal characteristics were compared between cohorts using χ^2 tests for independence. For reported pregnancy outcomes of live births, major birth defects and ≥ 3 minor birth defects, a point estimate of the relative risk (RR) and 95% CI for the adalimumab-exposed group versus each control group was computed. The primary outcome of major birth defects evaluated all pregnancies ending in at least one live birth, and secondarily all pregnancies with known outcome. Infants with ≥ 3 minor malformations were evaluated to identify any cases with the same three specific anomalies within each group. To estimate the cumulative probability of spontaneous abortion, only women who enrolled with <20 weeks of gestation were used for the Kaplan–Meier (KM) analysis. Cox proportional hazards models were used to estimate the HRs and 95% CIs.

RESULTS

Patients

Through 31 December 2012, adalimumab was administered to 15 152 patients in RA studies, representing 24 810 PYs of adalimumab exposure. Incidence rates presented in [table 1](#) include rates of both serious and non-serious AEs of interest.

Infections

SIEs were the most frequently reported SAEs, including pneumonia (0.7E/100 PYs), cellulitis (0.3E/100 PYs), bacterial arthritis and sepsis (0.2E/100 PYs each). The remaining SIEs were reported at $\leq 0.1E/100$ PYs.

At screening, 1272 (13.5%) patients were diagnosed with LTBI by a positive tuberculin skin test. During follow-up, 18 patients converted to LTBI status ($<0.01E/100$ PYs). Sixty-three active TB events occurred in 59 patients (0.3E/100 PYs).

In all RA studies, 40 opportunistic infections excluding oral candidiasis, HZ and TB were reported in 35 patients at a rate of 0.2E/100 PYs. The most frequently reported opportunistic infections were oesophageal candidiasis ($<0.1E/100$ PYs) and coccidiomycosis, cytomegalovirus infection and mycobacterium avium complex infection ($<0.1E/100$ PYs).

Influenza vaccination

In a post hoc analysis,⁷ vaccine use was evaluated in 553 patients with RA receiving ≥ 1 dose of adalimumab for up to 10 years (mean 5.6 years). One hundred and eighty patients (32.5%) received vaccinations at the discretion of the investigators (average disease duration, 14 years at first vaccination). Of these, 171 (30.9%) received at least one influenza vaccination, with a total of 351 influenza vaccinations administered. Influenza-related AEs occurred in 5% (8/171) of vaccinated patients compared with 14% (55/382) of patients not vaccinated during the study (see online supplementary figure S2).

Table 1 Incidence rates of adverse events of interest in patients with rheumatoid arthritis treated with adalimumab (N=15 152; 24,810.4 PYs)

Adverse events	E (E/100 PYs)
Serious infections	1154 (4.7)
Active tuberculosis (TB)	63 (0.3)
Opportunistic	14 (<0.1)
Zoster	19 (<0.1)
Non-serious infections	
Opportunistic infections, excluding oral candidiasis, herpes zoster and TB	26 (0.1)
Herpes zoster	424 (1.7)
Reactivation of hepatitis B*	3 (<0.1)

*Two patients experienced three events of hepatitis B reactivation: chronic hepatitis B, hepatitis B and viral hepatitis carrier.
E, number of events; E/100 PYs, events per 100 patient-years.

Laboratory parameters

Haematology

After 6 months of treatment, incidence of moderate anaemia (Hb 8.0 to <10 g/L) was significantly less in patients treated with adalimumab-plus-MTX for both early ($p<0.05$) and long-standing RA ($p<0.05$). Mean increases in Hb levels was higher in patients treated with adalimumab-plus-MTX in both early ($p<0.05$) and long-standing RA ($p<0.05$) ([table 2](#)).

Metabolic

At baseline, mean fasting TC, LDL and HDL were 4.974 mmol/L (192 mg/dL), 2.851 mmol/L (110 mg/dL) and 1.423 mmol/L (55 mg/dL), respectively, in the adalimumab-plus-MTX treatment group and 5.337 mmol/L (206 mg/dL), 3.146 mmol/L (121 mg/dL) and 1.562 mmol/L (60 mg/dL), respectively, in the MTX-monotherapy group. After 6 months, the mean changes in TC and LDL were higher in patients treated with adalimumab-plus-MTX compared with that of MTX-monotherapy (see online supplementary figure S1). Mean HDL changes were not different in the adalimumab-plus-MTX group compared with that of MTX-monotherapy. The increases in TC and LDL concentrations in both groups were mild and not clinically significant. At baseline, mean Apo A-1, Apo B and lipoprotein were 131, 81 and 20 mg/dL, respectively, in the adalimumab-plus-MTX group and 131, 81 and 21 mg/dL, respectively, in the MTX-monotherapy group. Mean Apo A-1, Apo B and lipoprotein changes were not different in the adalimumab-plus-MTX group compared with that of MTX-monotherapy.

Exposure during pregnancy

A total of 154 women (74 exposed to adalimumab, 80 with RA not exposed to adalimumab) enrolled in the OTIS registry. The mean gestational age at delivery of live births was similar between the two groups (38.5 vs 38.2 weeks, $p=0.30$). Of 74 pregnant women exposed to adalimumab, approximately 40%, 16% and 44% used adalimumab in the first trimester only, for two trimesters and throughout pregnancy, respectively. Per protocol, MTX was not allowed to be used concomitantly with adalimumab in the OTIS pregnancy registry. However, there were five patients using adalimumab-plus-methotrexate at inclusion into OTIS registry and none on MTX in the RA control population.

The frequencies and RR of major birth defects ([table 3](#)) were not different between adalimumab-exposed women, unexposed

Table 2 Frequency and mean change from baseline in Hb values at 6 months of treatment in two studies in patients with early RA,^{4 5} and one in long-standing patients with RA⁶

	Early RA		Long-standing RA	
	Placebo-plus-MTX N=774	Adalimumab-plus-MTX N=783	Placebo-plus-MTX N=200	Adalimumab-plus-MTX N=207
Anaemia				
Hb<10.0–8.0 g/dL	55 (7.1)	28 (3.6)*	11 (5.5)	3 (1.4)*
Hb<8.0–6.5 g/dL	4 (0.5)	2 (0.3)	0	0
Hb decreased				
Hb decrease 1.0–3.0 g/dL	263 (34.0)	176 (22.5)*	71 (35.5)	45 (21.7)*
Hb decrease >3.0 g/dL	3 (0.4)	0	1 (0.5)	2 (1.0)
Hb, mean change (g/dL)	-0.24	+0.45*	-0.18	+0.44*

Values are listed as n (%) unless otherwise indicated.
 *p<0.05 for adalimumab-plus-MTX versus MTX-monotherapy. χ^2 test for frequency rates.
 Hb, haemoglobin; MTX, methotrexate; RA, rheumatoid arthritis.

Table 3 Outcomes of pregnant women with RA exposed to adalimumab compared with pregnant women with RA not exposed to adalimumab and to pregnant women without autoimmune disease

	Adalimumab-exposed cohort	RA Comparison cohort	RR (95% CI)	Healthy cohort	RR (95% CI)
	N=74 n (%)	N=80 n (%)		N=219 n (%)	
Live births	65 (87.8)	74 (92.5)	0.95 (0.85 to 1.05)	198 (90.4)	0.97 (0.88 to 1.07)
Major birth defects among live births	3/65 (4.6)	4/74 (5.4)	0.75* (0.13 to 3.61)	10/198 (5.1)	0.91 (0.26 to 3.22)
Major birth defects among all pregnancies	3/72 (4.2)	5/77 (6.5)	0.72* (0.14 to 3.50)	10/202 (5.0)	0.77 (0.22 to 2.67)
≥3 Minor malformationst	12/45 (26.7)	18/64 (28.1)	1.15‡ (0.43 to 3.08)	31/123 (25.2)	1.06§ (0.41 to 2.53)

*Adjusted for RA disease severity (impairment) measure; adjusted OR and 95% CI is reported as an estimate of the adjusted RR and 95% CI.
 †Reflects the number with pattern of minor malformations among infants receiving dysmorphological examination.
 ‡Adjusted for maternal education, RA disease severity measures (impairment, pain) and sex of infant; adjusted OR and 95% CI are reported as estimates of the adjusted RR and 95% CI.
 §Adjusted for prednisone use; adjusted OR and 95% CI are reported as estimates of the adjusted RR and 95% CI.
 RA, rheumatoid arthritis; RR, relative risk.

women with RA and healthy women. Among the specific birth defects in the adalimumab cohort, no pattern was evident. Specific major birth defects in the adalimumab-exposed cohort were ventricular septal defect (resolved), microcephaly and undescended testicle. In the RA cohort, ventricular septal defect (resolved), microcephaly, talipes equinovarus, cataract (not otherwise specified (NOS)) and chromosomal anomaly NOS were observed. Likewise, rates of ≥3 minor birth defects were similar among the three cohorts, with no two infants in the adalimumab-exposed group having the same three specific minor anomalies.

The adjusted HR for spontaneous abortion in the adalimumab-exposed cohort relative to the RA comparison group was not significantly elevated (adjusted HR=2.06, 95% CI 0.53 to 7.98); however, the number of events was small (n=10). No stillbirths were reported in the adalimumab-exposed cohort. Preterm delivery occurred at similar rates between the adalimumab-exposed and RA comparison groups (adjusted HR=1.08, 95% CI 0.41 to 2.83).

DISCUSSION

Anti-TNF therapy is associated with an increased risk of infections. The spectrum of infections reported herein is similar to those reported with other anti-TNFs in both randomised clinical trials and registries,^{9–12} and the types of infections have not changed over time.^{2 13}

Opportunistic infections, although uncommon, may be challenging from a diagnostic perspective, given the variety of possible bacterial, mycobacterial, fungal, viral and parasitic agents.

Recently, there has been great interest in HZ.¹⁴ The overall rate with adalimumab was low and similar to reported rates in registries and a large claims database.^{14–16} This suggests that the use of anti-TNF therapies may not put patients at higher risk of HZ, but the risk:benefit for vaccination prior to initiating biological therapies remains compelling.

Overall, the effect of adalimumab on Hb and lipid parameters suggests no new safety signals in relation to MTX-monotherapy, in both early and long-standing RA.¹⁷ Monitoring lipid changes is of particular importance since risk of cardiovascular events may be increased in RA.

Routine vaccination of patients with RA with non-live agents, even in the setting of ongoing anti-TNF treatment, is recommended by the Advisory Committee on Immunization Practices.¹ However, awareness of this appears to be low, since a minority of patients with RA starting adalimumab in our studies received influenza vaccination. Patients that received this vaccine clearly presented with fewer influenza-related AEs over an average of 5.6 years of follow-up, compared with patients not receiving the vaccine.

Like other anti-TNFs, adalimumab is classified as pregnancy category B (no documented human toxicity) by the US Food and Drug Administration. A reproductive animal study revealed no evidence of fetal harm due to adalimumab,¹⁸ but only a small number of adalimumab-exposed human pregnancies have been published to date.^{19–21} The OTIS registry reported neither specific pattern of defects in adalimumab-exposed infants during prenatal development nor adverse pregnancy outcomes.

Strengths and limitations

Strengths of this adalimumab safety analysis include the number of patients, the duration of adalimumab exposure and the close monitoring in clinical trials compared with postmarketing surveillance or non-interventional studies. Our focus was on safety aspects that have not been broadly published with adalimumab or other anti-TNFs.

Limiting this analysis to clinical trial experience may not fully reflect clinical practice, due to selection bias of trial populations, survival of completers and comorbidities. Comparisons with other treatments are limited due to the lack of a control group with any specific active treatment.

CONCLUSIONS

The analysis of this large clinical trial database of patients with moderate to severe RA updates and confirms the known safety profile of adalimumab with regard to infections, laboratory abnormalities, hepatitis B reactivation and adverse pregnancy outcomes. Finally, the benefit of influenza vaccination for patients with RA is reinforced.

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