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Original article

Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy

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Abstract

Objective. To evaluate the long-term effectiveness and safety of 10 years of adalimumab (ADA) treatment in DMARD-refractory RA patients and to analyse efficacy based on RF status and baseline disease duration.

Methods. DE020 was a multicentre, phase 3, open-label continuation study. Adult RA patients who received s.c. ADA (40 mg every other week or monthly) in one of four early assessment studies could receive ADA for $\leqslant$10 years in DE020. Assessments included the 28-joint DAS with CRP (DAS28-CRP), Simplified Disease Activity Index (SDAI), HAQ Disability Index (HAQ-DI) and safety as events per 100 patient-years.

Results. Of 846 enrolled patients, mean age at baseline was 55.6 years, 78.1% were women, mean disease duration was 11.7 years and 27.0% were RF$^-$. Among 286 (33.8%) patients who completed 10 years of ADA, 168/236 (71.2%) achieved DAS28-CRP $\leqslant$3.2, 101/238 (42.4%) achieved HAQ-DI $<$0.5 and 90/241 (37.3%) achieved DAS28-CRP $\leqslant$3.2 plus HAQ-DI $<$0.5. DAS28-CRP- or SDAI-based remission was observed in 135/236 (57.2%) and 70/236 (29.7%) patients, respectively. Effectiveness outcomes were similar regardless of RF status. Higher proportions of patients with shorter *vs* longer baseline disease duration ($\leqslant$2 *vs* $>$2 years) achieved HAQ-DI $<$0.5 (60.6% *vs* 39.5%; $P = 0.023$) and DAS28-CRP $\leqslant$3.2 plus HAQ-DI $<$0.5 (58.1% *vs* 32.5%; $P = 0.006$). Adverse events (317.2 events per 100 patient-years) during ADA exposure were consistent with the expected safety profile for TNF inhibitors.

Conclusion. ADA led to sustained clinical and functional responses in the 33.8% of treatment-refractory RA patients who completed 10 years of treatment. Patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. Trial registration: ClinicalTrials.gov, http://www.clinicaltrials.gov, NCT00195650.

Key words: adalimumab, long-term therapy, rheumatoid arthritis.

CLINICAL SCIENCE

Rheumatology key messages

- Ten year adalimumab treatment led to clinical and functional improvements in patients with DMARD-refractory RA.
- Safety findings from 5224 patient-years of adalimumab exposure in RA were as expected.
- RA patients with shorter disease duration (i.e. earlier treatment) achieved better long-term outcomes with adalimumab.

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Introduction

RA is a chronic inflammatory disorder of the joints, with a reported prevalence of ~0.5–1% worldwide [1]. RA is associated with substantial morbidity and mortality. Recommendations formulated by the EULAR and ACR for the management of RA are aimed at achieving remission or low disease activity (LDA) [2, 3]. First-line treatment includes conventional synthetic DMARDs; in particular, MTX. If disease control or a target is not achieved within the first 6 months of treatment, recommendations suggest treatment with a second DMARD or the addition of a biologic DMARD if poor prognostic factors are present. Because RA is a chronic disease, patients may require continued, long-term therapy with biologic DMARDs in order to suppress disease activity, prevent structural progression and maintain physical function. Considering the likelihood of lifelong therapy, studies reporting long-term effectiveness and safety observations with biologic DMARDs are warranted.

Disease characteristics, such as the presence of autoantibodies, high disease activity and early joint damage, have been shown to impact effective management of RA [3]. In addition, therapeutic response may be influenced by disease duration at the time of treatment initiation. For example, there appears to be a window of opportunity for adding a TNF inhibitor to standard therapy; a delay of >2 years has been shown to result in a suboptimal clinical response [4, 5]. Thus a better understanding of the impact of disease duration on clinical outcomes is needed, particularly in patients who have failed several DMARD therapies.

The TNF inhibitor adalimumab (ADA), either as monotherapy or in combination with MTX, has demonstrated efficacy and safety in patients with RA in multiple studies [4–9]. This study (DE020) was a long-term extension of four studies (DE005/DE005X, DE009/DE009X, DE031 and DE037) that were conducted in the early development programme of ADA [8, 10–12]. All four studies enrolled patients with active RA and an inadequate response to MTX and/or other DMARDs. We report the final 10 year results from DE020 on the long-term effectiveness and safety of adalimumab exposure in patients with RA and previous DMARD failure. Further objectives of this *post hoc* analysis were to assess the long-term effectiveness of ADA in patients with RA on the basis of RF status and baseline disease duration.

Methods

Study design and patients

DE020 was a 10 year, multicentre, phase 3, open-label continuation study (NCT00195650) evaluating the long-term effectiveness, safety and tolerability of ADA in patients with RA. Adults with RA who completed one of four ADA studies conducted in the USA or Canada (DE005/DE005X, DE009/DE009X, DE031 or DE037) were eligible for enrolment in this rollover study. Patients with known HIV infection, a history of tuberculosis (TB) or listeriosis, any ongoing chronic or active infection, chronic use of oral antibiotics or any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 30 days of study entry were excluded. Patients received s.c. injections of ADA 40 mg every other week (eow) for up to 10 years. Patients who had received monthly dosing in their initial study continued monthly dosing in DE020. In addition, any patients who received ADA eow in the current study and maintained a 50% improvement in ACR criteria (ACR50) for two consecutive visits could change to monthly dosing. In contrast, patient dosing frequency could be increased to ADA 40 mg/week in response to any increase in disease activity. Concomitant DMARD therapy was allowed at the discretion of the investigator. The study was approved by 21 institutional review boards and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, US Food and Drug Administration regulations governing clinical study conduct and principles that have their origin in the Declaration of Helsinki. All patients provided written informed consent prior to study initiation.

Effectiveness assessments

Clinical and functional responses to ADA treatment were assessed at year 10. Clinical effectiveness was assessed by the ACR20, ACR50 and ACR70 criteria [13], the 28-joint DAS based on CRP (DAS28-CRP) [14, 15], the Simplified Disease Activity Index (SDAI) [16] and CRP concentration. The proportions of patients with clinical responses were compared based on achieving the ACR criteria, DAS28-CRP LDA or remission (score $\leqslant$3.2 or <2.6, respectively), SDAI remission (score $\leqslant$3.3) and CRP concentration $\leqslant$1.0 mg/dl. Physical function was assessed using the HAQ Disability Index (HAQ-DI) [17]. Normal physical function was defined as HAQ-DI <0.5. Combined clinical and functional response was assessed as the percentage of patients achieving simultaneous LDA and normal function (DAS28-CRP$\leqslant$3.2 and HAQ-DI <0.5).

Safety assessments

All patients who received one or more doses of study drug were included in the safety analysis. Safety was assessed in terms of adverse event (AE) incidence and events per 100 patient-years (E/100-PYs). Treatment-emergent AEs (TEAEs) were defined as AEs occurring from the date of the first dose of ADA in DE020 until 70 days after the last dose of ADA. TEAEs were coded according to the Medical Dictionary for Regulatory Activities, version 14.0, and analysed by severity and relationship to the study drug. A serious AE was defined as hospitalization, significant disability/incapacity, congenital anomaly, new diagnosis of cancer, life-threatening event or death.

Statistical analyses

Results of this *post hoc* analysis are reported through 10 years of ADA treatment. All patients who had one or more effectiveness measurement after the first dose of study drug in DE020 were included in the intent-to-treat (ITT) population. Baseline and demographic data and numbers

of patients achieving effectiveness endpoints were summarized descriptively. Nonresponder imputation was used as a sensitivity analysis to account for discontinuations during the 10 year study for the ITT population. For analyses using observed data, only patients with nonmissing values were included. The impact of several baseline variables, including sex, age, body weight, CS use, RF status (positive or negative) and disease duration ($\leqslant$2 or $>$2 years) on 10 year effectiveness outcomes was also assessed. Differences in effectiveness outcomes between disease duration and RF status subgroups were analysed using the Pearson chi-square test or Fisher's exact test.

Results

Patients

Of the 846 patients in the ITT population of DE020, 321 (37.9%) completed the study and 286 (33.8%) received a full 10 years of ADA treatment (Fig. 1A). Overall, there was an increase in discontinuation ~6 months after the study began, followed by a fairly linear rate of withdrawal afterwards of approximately $\leqslant$10% annually; the rate of discontinuation was statistically similar regardless of baseline disease duration (Fig. 1B). Baseline demographics and disease characteristics in the initial studies were typical for patients with chronic RA (Table 1). Most patients were women (78.1%); the mean baseline age of patients was 55.0 years in the initial studies and 55.6 years in the current study. The majority of patients (95.9%) had been treated with DMARDs prior to participation in the initial studies; 73.0% of patients were seropositive for RF. Before participation in the initial studies, the majority of patients (86.0%) had a disease duration of $>$2 years. Patients had more severe disease activity at baseline in the initial studies compared with the current study (Table 1). Most patients began the study with 40 mg eow dosing of ADA [n = 829 (98.0%)], 17 (2.0%) patients were on monthly ADA and 31 patients (3.7%) switched from eow to monthly dosing during the course of the study. Concomitant use of a nonbiologic DMARD for RA or an NSAID or CS for any reason occurred in 89.2%, 85.6% and 80.1% of patients, respectively, at some point during this 10 year study. The reasons for discontinuation were AE development [n = 194 (22.9%)], lack of efficacy/disease progression [n = 99 (11.7%)], administrative reason [n = 83 (9.8%)], withdrawal of consent [n = 67 (7.9%)], loss to follow-up [n = 44 (5.2%)], death [n = 23 (2.7%)] and protocol violation [n = 15 (1.8%)]. Among the 194 patients who withdrew from the study due to AEs, 185 stopped study treatment permanently.

Effectiveness outcomes

Clinical and functional improvements in ACR responses, DAS28-CRP, HAQ-DI, SDAI and serum CRP levels persisted over the course of the study with ADA treatment, based on observed data at each time point (Fig, 2; solid symbols). Based on observed data at year 10, ACR20, ACR50 and ACR70 responses were achieved by 78.6%, 55.5%, and 32.8% of treatment completers, respectively (Fig. 2A; solid symbols). Remission, defined as DAS28-CRP $<$2.6 or SDAI $\leqslant$3.3, was observed for 57.2% and 29.7% of treatment completers, respectively, at year 10 (Fig. 2B; solid circle and square). LDA, defined as DAS28-CRP $\leqslant$3.2, was achieved by 71.2% of treatment completers at year 10 (Fig. 2C; solid circle); the only statistically significant baseline and week 24 predictors of LDA at 10 years, based on logistic regression, were male sex [odds ratio (OR) 3.023 (95% CI 1.096, 8.340), P = 0.033] and DAS28 at week 24 [OR 0.424 (95% CI 0.194, 0.928), P = 0.032]. At year 10, 42.4% of treatment completers had normal physical function (HAQ-DI $<$0.5) and 37.3% exhibited both LDA and normal function (Fig. 2C; solid square and triangle). Suppression of CRP concentration to $\leqslant$1.0 mg/dl was achieved by 92.9% of patients after completing 10 years of treatment (Fig. 2D; solid circle).

Based on non-responder imputation, the response rate for each effectiveness outcome gradually decreased over the course of the study, corresponding to the steady rate of treatment discontinuation (Fig. 2; open symbols). The observed effectiveness outcome response rates at the final visit generally remained high (Fig. 2; bars within inset plots).

Among the ITT patients who completed 10 years of ADA treatment, those with normal physical function at year 10 had consistently lower DAS28-CRP scores over the course of the study compared with those without normal function at year 10 (Fig. 3). Among 836 ITT patients with observed HAQ-DI and DAS28-CRP data, time-averaged physical function [area under the time curve (AUC) for HAQ-DI] was most favourable among patients who achieved remission (DAS28-CRP $<$2.6; n = 266; mean AUC of HAQ-DI 154.6). Time-averaged physical function was comparable among patients who achieved LDA (DAS28-CRP $\geqslant$2.6–$\leqslant$3.2; n = 178; mean AUC of HAQ-DI 283.4) or neither remission nor LDA (DAS28-CRP $>$3.2; n = 392; mean AUC of HAQ-DI 307.4).

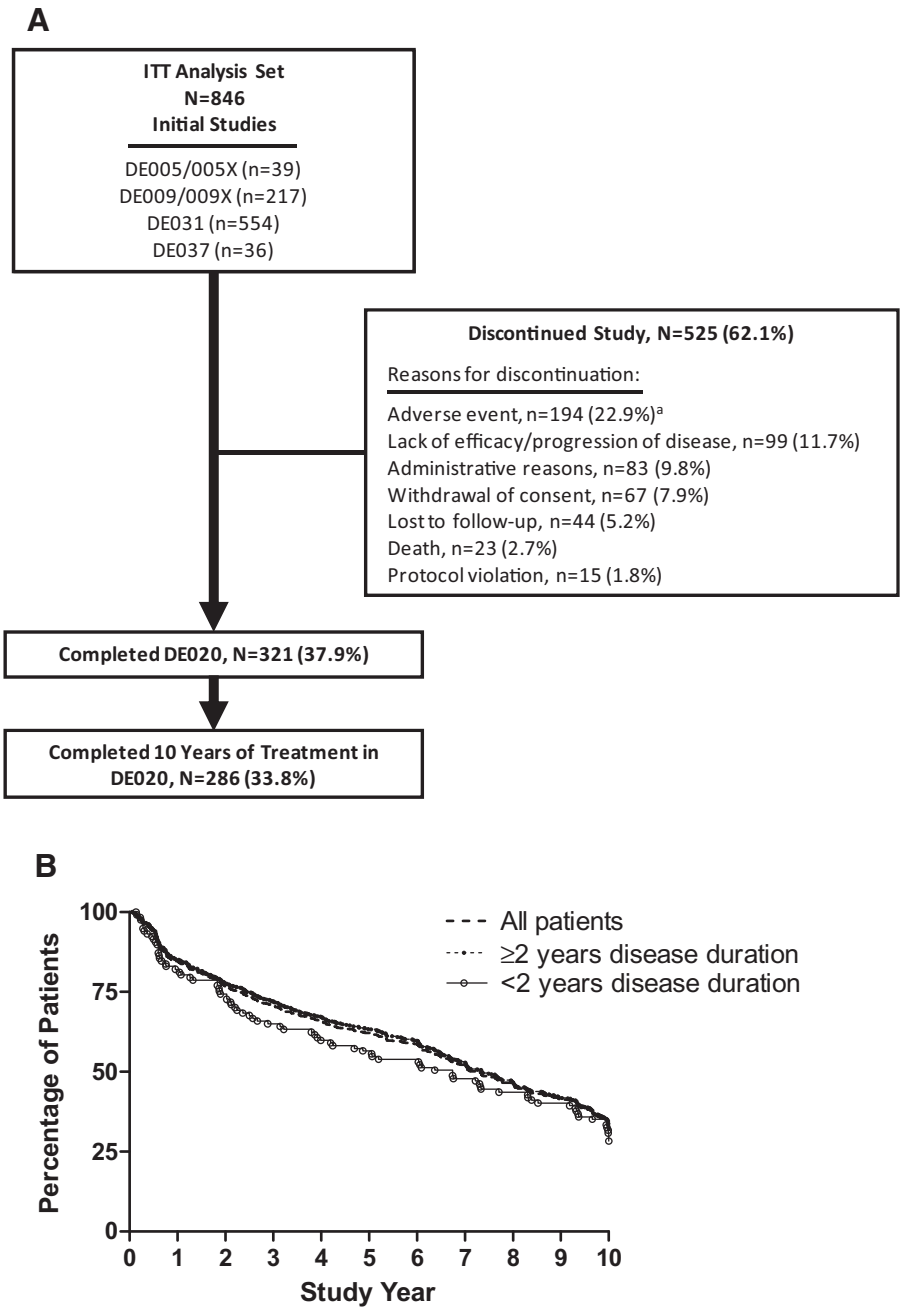
Effects of RF status

Based on RF status assessed at baseline of their initial study, identical proportions of RF^- and RF^+ ITT patients completed 10 years of ADA treatment (33.8% each; Table 2). Clinical and functional responses were generally similar among patients regardless of RF status (Table 2). Larger proportions of RF^- than RF^+ patients achieved an ACR50 response (63.2% *vs* 52.4%) or remission according to DAS28-CRP (63.6% *vs* 54.7%), although these differences were not statistically significant. No differences were observed between RF^- and RF^+ patients when the normal physical function criterion was combined with LDA.

Effects of baseline disease duration

Similar proportions of ITT patients with baseline disease duration $\leqslant$2 or $>$2 years completed 10 years of ADA treatment (32.2% *vs* 34.1%, respectively; Table 2). A significantly greater proportion of patients with baseline disease duration $>$2 *vs* $\leqslant$2 years were receiving concomitant DMARDs at the start of DE020 (86.2% *vs* 75.4%;

FIG. 1 Patient (**A**) disposition and (**B**) discontinuation over the course of the 10-year study



[a]Nine patients withdrew from the study due to adverse events but did not permanently discontinue treatment.

$P = 0.004$); there were no significant differences in systemic CS use. At initial study entry, patients with longer disease duration were significantly more likely to be RF^+ than patients with shorter disease duration (74.6% *vs* 64.4%; $P = 0.021$) and were significantly older on average at initial study entry (mean age 55.5 *vs* 51.8 years; $P = 0.002$) and at the start of DE020 (mean age 56.2 *vs* 52.4 years; $P = 0.002$). Response rates for effectiveness outcomes were consistently numerically higher among patients with shorter baseline disease duration (Table 2). Of note, the proportion of patients achieving an ACR50 response at 10 years was statistically greater among patients with baseline disease duration $\leqslant 2$ years compared with >2 years (71.9% *vs* 52.9%, respectively; $P = 0.045$); a trend was also observed for ACR70 response (46.9% *vs* 30.6%, respectively; $P = 0.068$). A statistically significant difference was observed in the proportion of patients who achieved normal function with a disease duration

Table 1 Demographics and baseline characteristics

	Initial study	Current study
Women, *n* (%)	661 (78.1)	661 (78.1)
Age at first dose, years	55.0 (12.2)	55.6 (12.2)
Race, *n* (%)		
White	734 (86.8)	734 (86.8)
Black	41 (4.8)	41 (4.8)
Hispanic	43 (5.1)	43 (5.1)
Other	28 (3.3)	28 (3.3)
Duration of RA, years	11.1 (9.5)[a]	11.7 (9.6)[a]
⩽2 years, *n* (%)	118 (14.0)[a]	90 (10.7)[a]
>2 years, *n* (%)	727 (86.0)[a]	755 (89.3)[a]
Prior DMARD use for RA, *n* (%)	811 (95.9)	NA
MTX	709 (83.8)	NA
HCQ	433 (51.2)	NA
SSZ	239 (28.3)	NA
Gold	154 (18.2)	NA
LEF	120 (14.2)	NA
Prior CS use for any reason, *n* (%)	476 (56.3)	NA
Prior NSAID use for any reason, *n* (%)	681 (80.5)	NA
Presence of morning stiffness		
Yes, *n*/*N*[b] (%)	556/590 (94.2)	573/842 (68.1)
TJC, 68 joints	27.9 (13.2)	13.3 (14.3)
SJC, 66 joints	20.1 (10.4)	10.5 (10.9)
TJC, 28 joints	15.1 (6.6)	6.8 (7.3)
SJC, 28 joints	13.5 (5.8)	7.2 (6.6)
PtGA pain, 100 mm VAS	54.4 (22.2)	33.4 (25.3)
PtGA disease activity, 100 mm VAS	53.5 (22.8)	32.2 (24.6)
PGA, 100 mm VAS	59.2 (16.5)	29.6 (22.3)
CRP, mg/l	18.0 (21.4)	10.0 (15.3)
RF status negative,[c] *n* (%)	228 (27.0)	NA
HAQ-DI	1.4 (0.6)	0.9 (0.7)
DAS28-CRP	5.7 (0.9)[d]	3.9 (1.5)

Data are mean (S.D.) unless otherwise indicated. [a]$n = 845$. [b]*n* indicates the number of patients without missing values. [c]Not assessed before the first dose of open-label adalimumab in the current study. [d]$n = 844$. DAS28-CRP: 28-joint DAS with CRP; HAQ-DI: HAQ Disability Index; NA: not available; PGA: physician's global assessment of disease activity; PtGA: patient's global assessment of disease activity; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

⩽2 years compared with >2 years at baseline (60.6% *vs* 39.5%, respectively; $P = 0.023$). The percentage of patients achieving simultaneous LDA and normal function was also statistically greater among patients with baseline disease duration ⩽2 years compared with >2 years (58.1% *vs* 32.5%; $P = 0.006$).

Long-term ACR20 non-responders

Nine patients never achieved an ACR20 response and yet continued in the study for at least 5 years. The degree of improvement in individual components of the ACR response criteria for these patients is presented in supplementary Table S1, available at *Rheumatology* Online. Each patient showed some level of improvement in at least one of the individual component measures. The majority of these patients experienced ⩾20% improvements in patient-reported measures of disease activity and/or pain.

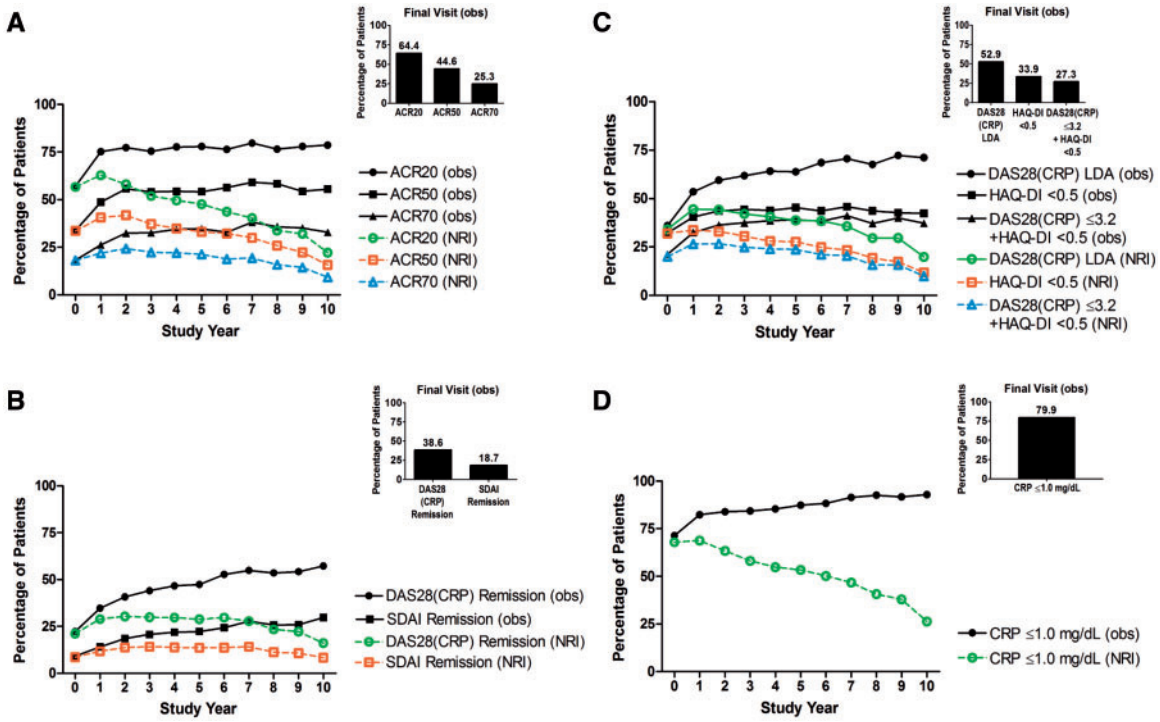
Safety

All 846 patients enrolled in the study received one or more injections of ADA. The mean duration of ADA exposure was 6.2 years (median 7.1 years), which totalled 5224 patient-years of exposure. The majority of patients (95.5%) reported one or more TEAEs during the 10 year study (Table 3). Approximately half of patients experienced a severe TEAE (51.2%; 22.8 E/100-PYs) or a serious TEAE (51.1%; 18.2 E/100-PYs). A TEAE considered at least possibly related to the study drug was experienced by 69.0% of patients (52.7 E/100-PYs). TEAEs led to permanent study drug discontinuation in 22.3% of patients and a dose reduction in 1.3% of patients. Four of the 189 patients who permanently discontinued study treatment due to TEAEs withdrew from the study for other reasons (two deaths and two withdrawals of consent). The majority of TEAEs that occurred in ⩾10% of patients (supplementary Table S2, available at *Rheumatology* Online) are consistent with the safety profile for ADA, are associated with RA or are common in a middle-aged population. Upper respiratory tract infection (46.3%), RA disease flare (34.0%) and sinusitis (25.1%) were the most frequently reported TEAEs.

Over the course of the 10 year study, 125 patients had serious infections (3.1 E/100-PYs; Table 3). Serious infections reported by ⩾2% of patients were cellulitis (2.4%) and pneumonia (4.3%). Opportunistic infections occurred in eight patients (0.9%) and included oesophageal candidiasis ($n = 3$), coccidioidomycosis ($n = 2$), *Mycobacterium avium* complex infection ($n = 1$), nocardiosis ($n = 1$) and systemic *Candida* ($n = 1$). Over the 10 year period, two cases of TB were reported (0.1 E/100-PYs); both were serious and one was severe. One case of TB occurred in a 41-year-old woman 1286 days after the first dose of ADA in the current study; another case occurred in a 68-year-old woman 388 days after the first dose of ADA in the current study. Both cases were considered probably related to the study drug and led to study discontinuation.

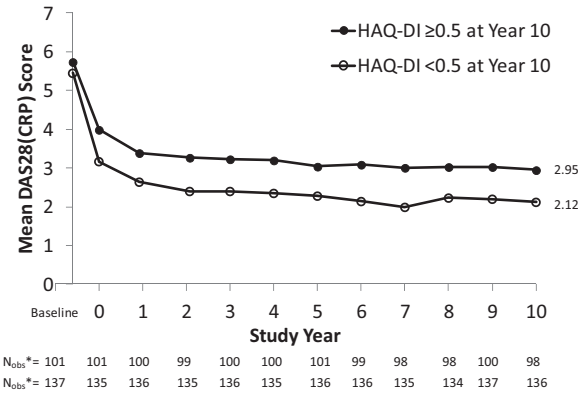
Treatment-emergent malignancies were reported in 14.8% of patients; 6 patients reported leukaemia (0.7%; 0.1 E/100-PYs), 9 patients reported lymphoma (1.1%; 0.2 E/100-PYs) and 10 patients reported melanoma (1.2%; 0.2 E/100-PYs). A total of 56 patients reported a treatment-emergent non-melanoma skin cancer (NMSC) event (6.6%; 1.5 E/100-PYs). Most malignancies were considered by the investigator as unrelated or unlikely to be related to the study drug. The standardized incidence ratio (SIR) for all malignancies was 1.14 [66 observed/57.68 expected (95% CI 0.88, 1.46)]. The SIR was 2.69 [6 observed/2.23 expected (95% CI 0.98, 5.86)] for

FIG. 2 Clinical and functional responses through year 10 (NRI, obs) and the final visit (obs)



(**A**) ACR20, ACR50 and ACR70. (**B**) DAS28-CRP remission (<2.6); SDAI remission (⩽3.3). (**C**) DAS28-CRP LDA (⩽3.2); normal function (HAQ-DI <0.5); simultaneous DAS28-CRP LDA (⩽3.2) and normal function (HAQ-DI <0.5). (**D**) CRP ⩽1.0 mg/dl. ACR20, 50, 70: 20, 50 or 70% improvement, respectively, in ACR criteria; DAS28-CRP: 28-joint DAS with CRP; HAQ-DI: HAQ Disability Index; LDA: low disease activity; NRI: non-responder imputation; obs: observed; SDAI: Simplified Disease Activity Index.

FIG. 3 Mean DAS28-CRP scores over time for patients with HAQ-DI ⩾0.5 or <0.5 at year 10



DAS28-CRP: 28-joint DAS with CRP; HAQ-DI: HAQ Disability Index.

melanoma and 2.12 [65 observed/30.60 expected (95% CI 1.64, 2.71)] for NMSC.

The incidence rates of myocardial infarction, cerebrovascular accident and congestive heart failure were 0.4, 0.8 and 0.6 E/100-PYs, respectively, during this study.

A total of 35 patients died over the course of the study, and 25 deaths occurred during or within 70 days of ADA treatment. Most treatment-emergent deaths were considered unrelated or likely unrelated to treatment with ADA (supplementary Table S3, available at *Rheumatology* Online). Five patient deaths were deemed possibly related to the study drug, including one patient each with acute myeloid leukaemia, breast cancer, non-small cell lung cancer, metastases to the liver and sepsis. Overall, the standardized mortality ratio (SMR) was 0.76 (95% CI 0.53, 1.05). Using the 25 treatment-emergent deaths, the SMR was 0.54 (95% CI 0.35, 0.80). These SMRs indicate that long-term exposure to ADA was not associated with increased mortality in this patient population.

Discussion

The DE020 study was conceived with the goal of long-term follow-up, with effectiveness and safety data over 10 years in patients with DMARD-refractory RA; a strength of this final report is that it includes 5224 patient-years of prospective follow-up. As expected, long-term treatment with ADA reduced disease activity and improved physical function in patients who continued in the study. At year 10, the majority of patients exhibited LDA, and over half of the

Table 2 Proportion of patients achieving clinical and functional response at year 10 by RF status and baseline disease duration

	RF status ($n = 846$), n/N_{obs}[a] (%)		Baseline disease duration ($n = 845$), n/N_{obs}[a] (%)	
	RF$^-$	RF$^+$	⩽2 years	>2 years
Completed 10 years	77/228 (33.8)	209/618 (33.8)	38/118 (32.2)	248/727 (34.1)
ACR20	53/68 (77.9)	134/170 (78.8)	26/32 (81.3)	161/206 (78.2)
ACR50	43/68 (63.2)	89/170 (52.4)	23/32 (71.9)	**109/206 (52.9)***
ACR70	23/68 (33.8)	55/170 (32.4)	15/32 (46.9)	63/206 (30.6)
LDA, DAS28-CRP ⩽3.2	49/66 (74.2)	119/170 (70.0)	26/31 (83.9)	142/205 (69.3)
DAS28-CRP remission (<2.6)	42/66 (63.6)	93/170 (54.7)	21/31 (67.7)	114/205 (55.6)
Normal function, HAQ-DI <0.5	30/66 (45.5)	71/172 (41.3)	20/33 (60.6)	**81/205 (39.5)****
DAS28-CRP ⩽3.2 + HAQ-DI <0.5	25/64 (39.1)	59/170 (34.7)	18/31 (58.1)	**66/203 (32.5)*****
SDAI remission (⩽3.3)	22/66 (33.3)	48/170 (28.2)	13/31 (41.9)	57/205 (27.8)
CRP ⩽1.0, mg/dl	62/67 (92.5)	160/172 (93.0)	32/34 (94.1)	190/205 (92.7)

Bold values showed a statistically significant difference when compared between patients with ⩽2 *vs* >2 years of baseline disease duration. [a]N_{obs} indicates the number of patients with non-missing values. *$P = 0.045$ for the difference between subgroups; **$P = 0.023$ for the difference between subgroups; ***$P = 0.006$ for difference between subgroups (Pearson chi-square test or Fisher exact test). ACR20, 50, 70: 20, 50 or 70% improvement, respectively, in ACR criteria; DAS28-CRP: 28-joint DAS with CRP; HAQ-DI: HAQ Disability Index; LDA: low disease activity; SDAI: Simplified Disease Activity Index.

Table 3 Overview of treatment-emergent adverse events

	Incidence ($n = 846$), n (%)	E/100-PYs (ADA exposure = 5224 PYs), n (%)
Any AE	808 (95.5)	16 568 (317.2)
At least possibly drug-related AE	584 (69.0)	2753 (52.7)
Severe or life-threatening AE	433 (51.2)	1193 (22.8)
Serious AE	432 (51.1)	953 (18.2)
Fatal treatment-emergent AE	25 (3.0)	25 (0.5)
Deaths, including non-treatment emergent deaths	35 (4.1)	35 (0.7)
AE leading to permanent discontinuation of study drug	189 (22.3)[a]	239 (4.6)
AE leading to study drug dose reduction	11 (1.3)	12 (0.2)
Infections	678 (80.1)	4485 (85.9)
Serious infections	125 (14.8)	162 (3.1)
Opportunistic infections excluding TB and oral candidiasis	8 (0.9)	10 (0.2)
Serious opportunistic infections excluding TB and oral candidiasis	3 (0.4)	3 (0.1)
Active TB	2 (0.2)	3 (0.1)
Parasitic infections other than opportunistic infection	4 (0.5)	4 (0.1)
Malignancies	125 (14.8)	160 (3.1)
Lymphoma	9 (1.1)	10 (0.2)
NMSC	56 (6.6)	79 (1.5)
Malignancies other than lymphoma and NMSC	67 (7.9)	71 (1.4)
Malignancies other than NMSC	75 (8.9)	81 (1.6)
HSTCL	0	0
Leukaemia	6 (0.7)	6 (0.1)
Melanoma	10 (1.2)	10 (0.2)
Demyelinating disorder	5 (0.6)	5 (0.1)
Cerebrovascular accident	33 (3.9)	44 (0.8)
Congestive heart failure	27 (3.2)	33 (0.6)
Myocardial infarction	20 (2.4)	22 (0.4)
Injection-site reaction	116 (13.7)	210 (4.0)
Hepatic event	20 (2.4)	24 (0.5)
Elevated ALT levels	86 (10.2)	173 (3.3)

[a]One patient was found to have permanently discontinued from the study due to melanoma *in situ* after the database lock and is not reflected in the *n* (%) or E/100-PYs for permanent discontinuation of the study. ADA: adalimumab; AE: adverse event; ALT: alanine transaminase; E/100-PYs: events per 100 patient-years; HSTCL: hepatosplenic T cell lymphoma; NMSC: non-melanoma skin cancer; PY: patient-years; TB: tuberculosis.

patients were in remission according to DAS28-CRP. When using SDAI-based criteria, the number of patients in remission was lower, but still clinically relevant. Despite long-standing disease, normal physical function was observed for >40% of patients, and more than one-third of patients attained simultaneous normal function and LDA.

The safety profile of ADA, observed using combined data from 10 years of treatment in the current study, demonstrated no new findings compared with earlier reports [18, 19]. As is usual in long-term studies of biologics [20–25] and non-biologic DMARDs [26, 27], TEAEs were common.

Approximately 80% of patients experienced treatment-emergent infections, with a rate of 85.9 E/100-PYs. Serious infections in ADA-treated patients occurred at a rate of 3.1 E/100-PYs, which is slightly lower than rates observed in published trials of TNF inhibitors (4.2–6.4 E/100-PYs) [19, 21, 28], but is consistent with other reports in the literature [29]. Of interest, two patients developed active TB and eight patients had other opportunistic infections over the 10 year period of DE020. Although patients were screened before study entry, they were not routinely rescreened on an ongoing basis for TB or other opportunistic infections; these infrequent events reflect the low rates of mycobacterial TB and other opportunistic infections in the USA, even among those using TNF inhibitors.

Approximately 15% of patients experienced a treatment-emergent malignancy. In the current study, the SIR for overall malignancies was 1.14, with 95% CIs that encompassed 1, compared with the Surveillance, Epidemiology, and End Results (SEER) data for individuals without RA. Similarly the SIR for overall malignancies (excluding NMSC) was not elevated [0.64 (95% CI 0.53, 0.76)] in a 5 year observational study of 3435 patients with RA treated with ADA [30]. In contrast, the SIR was 1.28 (95% CI 1.10, 1.48) for malignancies observed in a cohort of 3771 patients with RA who were naive to biologic DMARDs compared with the general population in the UK [31]. The elevated SIRs for melanoma and NMSC in DE020 may reflect a more careful medical surveillance of patients in the study than is typical for individuals in the SEER database. However, the longitudinal data may militate against such an association, as the incidence of melanoma and NMSC did not increase with increasing ADA exposure (data not shown). SMRs indicate that long-term treatment with ADA was not associated with increased mortality in this patient population. The low incidences of myocardial infarction, cerebrovascular accident and congestive heart failure observed in this pre-selected population do not indicate an increased risk of these events with ADA use and are consistent with cardiovascular event rates reported in the Consortium of Rheumatology Researchers of North America database [32].

Similar percentages of patients with RF^+ and RF^- status completed 10 years of treatment with ADA. Clinical and functional response rates were generally similar between RF^- and RF^+ patients, although a greater proportion of RF^- patients achieved remission at year 10. These similarities support previous observations that RF status is not a conclusive predictor of response to anti-TNF therapy [33] or to MTX [34].

In the current study, patients with early disease, defined by convention as ⩽2 years of disease duration, achieved better clinical and functional responses. Normal function was reported to a greater extent among patients who began ADA treatment within 2 years of disease onset. Better outcomes for patients with shorter disease duration were not due to concomitant treatments, as patients with shorter disease duration had lower rates of DMARD use and similar rates of CS use. These results support the earlier initiation of effective therapy, including ADA, with the goal of improving long-term outcomes and limiting functional loss that seemingly cannot be recovered in patients with long-standing disease. Ten year results from the PREMIER trial led to similar conclusions [4].

This study had limitations that are characteristic of any open-label design; there also was bias towards responders, as only the patients who continued in the study were followed. Only 34% of the original cohort completed 10 years of ADA treatment and were included in the 10 year analysis, although similar completion rates were observed in patients with early RA (disease duration ⩽2 years; 32.2%) and established RA (disease duration >2 years; 34.1%), which may be expected due to these patients receiving the same long-term treatment. The overall 10 year treatment completion rate is comparable to the completion rates seen in the DE019 (44%) [7] and PREMIER (50%) [4] studies for patients who entered the open-label periods. Lack of effectiveness led ~12% of patients to discontinue study treatment. In addition, there are no radiographic data available; however, physical function was assessed.

In conclusion, 10 year treatment with ADA led to clinical and functional improvements in the 286 of 846 patients (34%) with DMARD-refractory RA who continued therapy throughout the entire study period. Safety findings from the 5224 patient-years of exposure are reassuring for infections, malignancies and cardiovascular outcomes; no new signals were found. RF status did not influence outcomes in this population, while those with shorter disease duration typically achieved better outcomes, underscoring the benefit of early treatment.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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