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CONCISE REPORT

Sustained improvements in MRI outcomes with abatacept following the withdrawal of all treatments in patients with early, progressive rheumatoid arthritis

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ABSTRACT

Objectives To assess structural damage progression with subcutaneous abatacept (ABA) in the *A*ssessing *V*ery *E*arly *R*heumatoid arthritis *T*reatment (AVERT) trial following abrupt withdrawal of all rheumatoid arthritis (RA) medication in patients achieving Disease Activity Score (DAS)-defined remission or low disease activity.

Methods Patients with early, active RA were randomised to ABA plus methotrexate (ABA/MTX) 125 mg/week, ABA 125 mg/week or MTX for 12 months. All RA treatments were withdrawn after 12 months in patients with DAS28 (C reactive protein (CRP)) <3.2. Adjusted mean changes from baseline in MRI-based synovitis, osteitis and erosion were calculated for the intention-to-treat population.

Results 351 patients were randomised and treated: ABA/MTX (n=119), ABA (n=116) or MTX (n=116). Synovitis and osteitis improved, and progression of erosion was statistically less with ABA/MTX versus MTX at month 12 (−2.35 vs −0.68, −2.58 vs −0.68, 0.19 vs 1.53, respectively; p<0.01 for each) and month 18 (−1.34 vs −0.49 −2.03 vs 0.34, 0.13 vs 2.0, respectively; p<0.01 for erosion); ABA benefits were numerically intermediate to those for ABA/MTX and MTX.

Conclusions Structural benefits with ABA/MTX or ABA may be maintained 6 months after withdrawal of all treatments in patients who have achieved remission or low disease activity.

Trial registration number NCT01142726; Results.

INTRODUCTION

Abatacept is a cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)–immunoglobulin G1 fusion protein[1] that selectively modulates the CD80/CD86:CD28 costimulatory pathway required for T-cell activation.[2] In people with rheumatoid arthritis (RA), treatment with abatacept has been shown to normalise levels of many inflammatory mediators associated with disease activity and progression.[1]

The *A*ssessing *V*ery *E*arly *R*heumatoid arthritis *T*reatment (AVERT) trial evaluated clinical remission at 12 months with subcutaneous abatacept plus methotrexate (MTX), abatacept monotherapy or MTX alone in patients with early RA and maintenance of remission following rapid withdrawal of all RA treatments.[3] Patients treated with abatacept in combination with MTX achieved higher rates of protocol-defined Disease Activity Score (DAS) remission (DAS28 C reactive protein (CRP) <2.6) versus MTX alone, and a small but significantly higher number of patients achieved sustained DAS-defined remission following withdrawal of all RA treatments.[3] The safety profile of abatacept, in combination with MTX or as monotherapy, was comparable with that of MTX alone.[3]

The AVERT trial evaluated clinical and also MRI outcomes. MRI is increasingly being used in clinical trials to assess the therapeutic efficacy and can detect early changes in inflammation—including synovitis, osteitis and joint damage—before radiographic joint erosion occurs;[4] in clinical studies, MRI measures of inflammation have even been shown to predict radiographic progression.[5–7] In patients with established RA, the benefits of abatacept in reducing synovitis and osteitis have previously been demonstrated using MRI.[8 9]

In this substudy of the AVERT trial, we report MRI measures of disease in patients with DAS-defined remission (DAS28 (CRP) <2.6) following 12 months of treatment and subsequent withdrawal of all RA medication, for up to 18 months.

METHODS

Study design and patient population

The trial design and primary results for AVERT (NCT01142726) have been described previously.[3] Briefly, patients were randomised (1:1:1) to receive abatacept 125 mg/week plus MTX, abatacept monotherapy (125 mg/week) or MTX alone for 12 months. At month 12, patients with DAS28 (CRP) <3.2 could enter the withdrawal period and all treatments for RA were stopped, with MTX and corticosteroids being tapered during the first month.

Assessments

All patients underwent contrast-enhanced 1.5 T MRI of the clinically most active wrist and hand (metacarpophalangeal joints 1–5) at baseline and at 6-month intervals thereafter; the same wrist/hand was imaged at each designated visit (see online

supplementary material). MRI assessments were evaluated at baseline and up to month 18; only patients with baseline and postbaseline MRI assessments were included (see online supplementary material).

Statistical analysis

Adjusted mean changes from baseline in MRI scores for synovitis, osteitis and erosion were calculated at months 12 and 18 in the intention-to-treat population, and analysed using a longitudinal repeated measures model adjusting for MRI score and corticosteroid use (yes/no) at baseline and presented by treatment group; observed data at all time points were included. For all mean response rates, SE, 95% CIs and p values were calculated (see online supplementary material).

The proportion of patients achieving DAS-defined remission and MRI non-progression (defined as change from baseline ≤smallest detectable change separately for erosion, osteitis and synovitis) was calculated at months 6, 12 and 18 as an exploratory endpoint (see online supplementary material). The percentage change in CRP from baseline was evaluated over time. Additionally, *post hoc* analyses included the number of patients achieving DAS-defined remission and MRI progression (defined as change from baseline >smallest detectable change) at month 18; the proportion of patients with a synovitis score >5 at baseline and at months 6, 12 and 18; and adjusted mean changes from baseline in MRI scores in the subgroup of patients who had DAS28 (CRP) <2.6 at both months 12 and 18.

RESULTS

Patient disposition and baseline characteristics

A total of 511 patients were enrolled, and 351 patients at 72 worldwide sites were randomly assigned (1:1:1) to treatment with abatacept plus MTX (n=119), abatacept monotherapy (n=116) or MTX (n=116). The proportion of patients with MRI assessments at baseline was 95.8% (114/119), 96.6% (112/116) and 95.7% (111/116), respectively; at baseline and month 12, it was 76.5% (91/119), 69.8% (81/116) and 72.4% (84/116), respectively; and at baseline, month 12 and month 18, it was 31.9% (38/119), 30.2% (35/116) and 25.0% (29/116), respectively. The average rate of missing MRI scores for those who had assessments at baseline was 16.9% over 12 months and 69.9% at 18 months. A total of 129/202 patients (63.9%) who entered the withdrawal period and who had MRI assessments at baseline and at month 12 discontinued during the withdrawal period (abatacept plus MTX, n=48 (37.2%); abatacept monotherapy, n=40 (31.0%); MTX, n=41 (31.8%)). The main reason for discontinuation was lack of efficacy (n=123/202; 60.9%). Clinical baseline characteristics for patients with MRI assessments at baseline and at month 12 were similar across treatment groups and were comparable with the overall AVERT population (table 1).

Table 1 Baseline characteristics for patients with MRI assessments at baseline and month 12

Characteristic	Abatacept plus MTX (n=91)	Abatacept monotherapy (n=81)	MTX (n=84)
Synovitis score	5.6 (4.2)	5.3 (3.8)	5.7 (4.2)
Osteitis score	4.4 (6.9)	4.3 (6.7)	3.4 (6.4)
Erosion score	7.2 (7.0)	5.1 (4.7)	6.3 (7.8)
Symptom duration, years	0.6 (0.5)	0.6 (0.5)	0.5 (0.5)
DAS28 (CRP)	5.5 (1.3)	5.5 (1.2)	5.3 (1.3)
HAQ-DI	1.5 (0.7)	1.4 (0.6)	1.4 (0.6)
Tender Joint Count (28 joints)	13.8 (7.8)	14.3 (7.7)	12.5 (7.7)
Swollen Joint Count (28 joints)	11.2 (7.1)	12.4 (7.6)	10.2 (6.9)
CRP, mg/L	17.5 (23.2)	16.6 (25.6)	16.0 (21.2)

Data are presented as mean (SD).
CRP, C reactive protein; DAS, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate.

Efficacy

Abatacept plus MTX resulted in significantly greater decreases from baseline in synovitis and osteitis scores on-treatment, and significantly less progression of erosion score on-treatment and following withdrawal of all therapies than MTX alone (figure 1). While mean MRI synovitis and osteitis scores increased following withdrawal of treatment in all three groups, the adjusted mean reductions from baseline with abatacept plus MTX at month 18 were still numerically greater than those with MTX alone (figure 1A, B). Changes in erosion score showed minimal difference between months 6 and 18 (figure 1C). Benefits of abatacept monotherapy were numerically intermediate to those of abatacept plus MTX and MTX alone. Cumulative probability plots for changes in MRI scores from baseline at month 12 are shown in online supplementary figure S1.

During study treatment, there was a reduction in the proportion of patients with active synovitis (score >5; indicative of active disease resulting in erosion progression[10]) in the abatacept plus MTX group versus that in the MTX alone group; at month 18, there was a numerical increase versus MTX alone (see online supplementary figure S1).

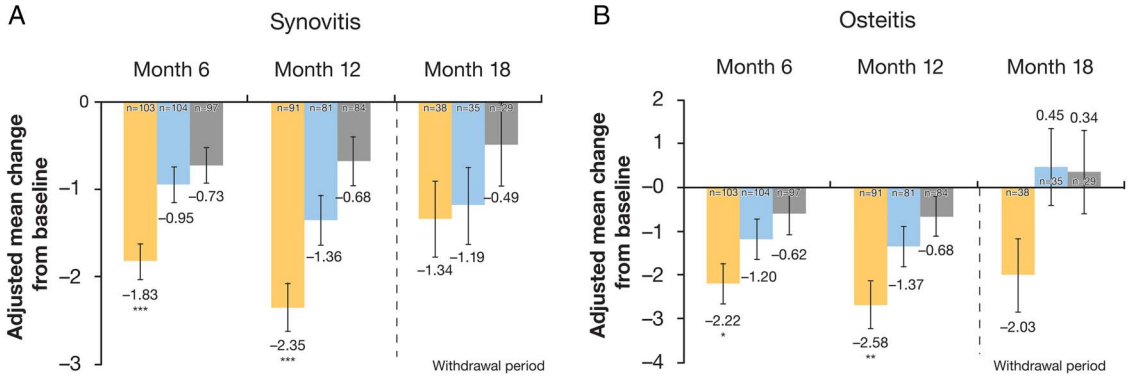
During study treatment, a statistically higher percentage of patients receiving abatacept plus MTX achieved DAS-defined remission together with MRI non-progression in synovitis, osteitis and erosion compared with those receiving MTX alone (table 2). Fewer patients in all three treatment groups achieved DAS-defined remission together with MRI non-progression after withdrawal of study drug compared with on-treatment (table 2). However, the percentages of patients in the abatacept plus MTX group were still approximately twice those of the MTX-alone group. The effect of abatacept monotherapy was numerically intermediate to that of abatacept plus MTX and MTX alone. In all treatment groups, a small number of patients still had MRI progression (see online supplementary material).

Post hoc analyses revealed that, in the small proportion of patients with DAS-defined remission at both months 12 and 18, MRI benefits achieved at month 12 were maintained up to month 18 (ie, after withdrawal of all therapies) in all three groups (see online supplementary figure S3).

Abatacept plus MTX treatment resulted in greater decreases from baseline in the inflammatory marker, CRP, during the treatment period and following the withdrawal of all therapies compared with MTX alone. Abatacept monotherapy and MTX alone had similar effects on CRP (see online supplementary table S1).

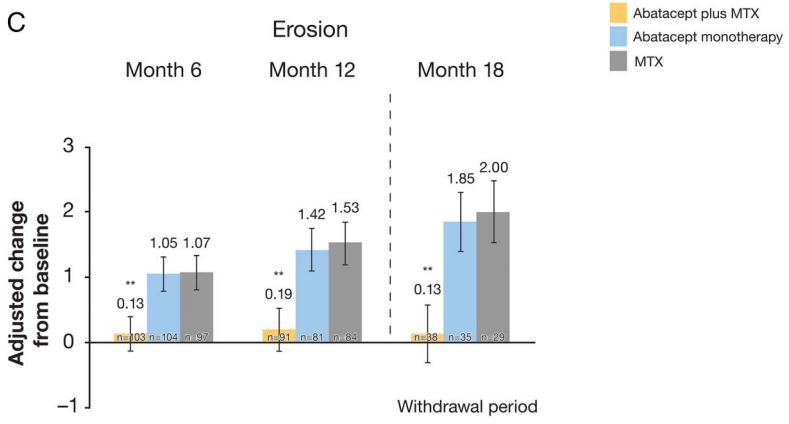
DISCUSSION

In this analysis of tissue effects, abatacept reduced inflammation and structural damage progression as assessed by changes in MRI scores (synovitis, osteitis and bone erosions) in patients with early and progressive RA. Following withdrawal of all therapies in patients with clinical disease activity, there was some reappearance of inflammatory activity in the joints. However, in those patients who maintained clinical remission or low disease



Adjusted mean treatment differences vs MTX (95% CI)			
	Month 6	Month 12	Month 18
Abatacept plus MTX	−1.10 (−1.64,−0.55); p=0.0001	−1.67 (−2.44,−0.91); p=0.0000	−0.85 (−2.12, 0.42); p=0.1865
Abatacept monotherapy	−0.22 (−0.76,−0.32); p=0.4290	−0.67 (−1.45, 0.10); p=0.0886	−0.70 (−1.99, 0.59); p=0.2849

Adjusted mean treatment differences vs MTX (95% CI)			
	Month 6	Month 12	Month 18
Abatacept plus MTX	−1.59 (−2.88, −0.31); p=0.0152	−1.90 (−3.15, −0.65); p=0.0031	−2.38 (−4.90, 0.15); p=0.0652
Abatacept monotherapy	−0.58 (−1.87, 0.71); p=0.3756	−0.69 (−1.95, 0.58); p=0.2861	0.10 (−2.47, 2.67); p=0.9364



Adjusted mean treatment differences vs MTX (95% CI)			
	Month 6	Month 12	Month 18
Abatacept plus MTX	−0.94 (−1.64, −0.23); p=0.0099	−1.34 (−2.25, −0.42); p=0.0044	−1.87 (−3.13, −0.60); p=0.0041
Abatacept monotherapy	−0.02 (−0.73, 0.69); p=0.9590	−0.11 (−1.03, 0.81); p=0.8142	−0.15 (−1.43, 1.14); p=0.8214

Figure 1 Adjusted mean change from baseline in MRI scores (ITT population). Change from baseline in (A) synovitis scores, (B) osteitis and (C) erosion at 6, 12 and 18 months. *p<0.05, **p<0.01 and ***p<0.001 for adjusted mean difference versus MTX at given time point. Error bars represent SEs. ITT, intention-to-treat; MTX, methotrexate.

activity following withdrawal of all RA therapy, this remission/low disease activity correlated with maintenance of inflammation control and structural benefits irrespective of initial treatment group. During both the treatment and withdrawal periods, improvements as assessed by MRI were greatest for abatacept plus MTX, followed by abatacept monotherapy and MTX monotherapy.

The improvements in MRI scores observed in the present study are consistent with previous abatacept studies[9 11] and recent randomised controlled trials of other biologics in patients with early or established RA (see online supplementary material).[12–16] The data presented here are also consistent with the maintenance of MRI benefits for 6 months following the withdrawal of abatacept in patients with early RA reported in the ADJUST trial.[9] Only a few studies of biologics have evaluated treatment withdrawal or de-escalation and imaging outcomes (MRI or radiography) in patients with RA.[17–20] Consistent with our study, Smolen *et al* showed that most patients with early RA (<1 year disease duration) who achieved a stable low-dose disease activity target at ~6 months maintained structural benefits, despite withdrawal of adalimumab. Similarly, induction treatment with MTX plus adalimumab was shown to result in fewer erosions at 1 year versus

Table 2 Proportion of patients with DAS28 (CRP) remission and MRI non-progression per MRI pathology over time (ITT population)

MRI pathology	Study time point (months)	Patients with DAS28 (CRP) remission* and MRI non-progression†			Abatacept plus MTX vs MTX estimate of difference (95% CI)	Abatacept monotherapy vs MTX estimate of difference (95% CI)
		Abatacept plus MTX (n=119)	Abatacept monotherapy (n=116)	MTX (n=116)		
Synovitis—n‡ (%) (95% CI)§	6	44 (37.0) (28.30 to 45.65)	32 (27.6) (19.45 to 35.72)	28 (24.1) (16.35 to 31.93)	12.84 (0.33 to 25.34); p=0.046	3.45 (−8.67 to 15.57); p=0.653
	12	59 (49.6) (40.60 to 58.56)	43 (37.1) (28.28 to 45.86)	41 (35.3) (26.65 to 44.04)	14.24 (0.88 to 27.59); p=0.038	1.72 (−11.50 to 14.95); p=0.891
	18	18 (15.1) (8.69 to 21.56)	11 (9.5) (4.15 to 14.81)	9 (7.8) (2.89 to 12.63)	7.37 (−1.55 to 16.29); p=0.117	1.72 (−6.36 to 9.81); p=0.815
Osteitis—n‡ (%) (95% CI)§	6	43 (36.1) (27.50 to 44.77)	32 (27.6) (19.45 to 35.72)	27 (23.3) (15.6 to 30.97)	12.86 (0.45 to 25.27); p=0.044	4.31 (−7.75 to 16.37); p=0.546
	12	58 (48.7) (36.76 to 57.72)	42 (36.2) (27.46 to 44.95)	41 (35.3) (26.65 to 44.04)	13.39 (0.04 to 26.75); p=0.052	0.86 (−12.34 to 14.06); p=1.000
	18	18 (15.1) (8.69 to 21.56)	12 (10.3) (4.80 to 15.89)	9 (7.8) (2.89 to 12.63)	7.37 (−1.55 to 16.29); p=0.117	2.59 (−5.65 to 10.82); 0.647
Erosion—n‡ (%) (95% CI)§	6	38 (31.9) (23.56 to 40.31)	30 (25.9) (17.89 to 33.83)	23 (19.8) (12.57 to 27.08)	12.11 (0.17 to 24.04); p=0.049	6.03 (−5.60 to 17.67); p=0.348
	12	51 (42.9) (33.97 to 51.75)	36 (31.0) (22.62 to 39.45)	33 (28.4) (20.24 to 36.66)	14.41 (1.46 to 27.36); p=0.030	2.59 (−10.04 to 15.21); p=0.774
	18	15 (12.6) (6.64 to 18.57)	11 (9.5) (4.15 to 14.81)	8 (6.9) (2.29 to 11.51)	5.71 (−2.68 to 14.10); p=0.210	2.59 (−5.32 to 10.50); p=0.632

*DAS-defined remission was defined as DAS28 (CRP) <2.6.
†MRI non-progression was defined as change from baseline ≤smallest detectable change. Smallest detectable change values used for non-progression: synovitis (2.01), osteitis (2.81) and erosion (2.29).
‡n=number of patients with DAS28 (CRP) remission and MRI non-progression.
§Normal approximation is used if the number of DAS28 (CRP) remission and MRI non-progression for all treatment arms was at least 5; otherwise an exact method was used.
CRP, C reactive protein; DAS, Disease Activity Score; ITT, intention-to-treat; MTX, methotrexate.

MTX alone in patients who discontinued adalimumab after 6 months' treatment.[17–20]

Some limitations of the present study should be taken into account. The *post hoc* analysis of change from baseline in MRI scores in patients with DAS28 (CRP) <2.6 at both months 12 and 18 had a small sample size, and therefore additional studies are needed to confirm these results, despite the sensitivity of MRI for detecting change. Additionally, the study was not powered to compare abatacept combination therapy with monotherapy.

In conclusion, these data from the AVERT study demonstrate that abatacept reduces inflammation and structural damage progression as assessed by MRI, and extends the current understanding of the effect of abatacept on synovium and bone. The withdrawal of abatacept therapy after achieving remission in some patients with early, progressive RA appears to be possible without an associated risk of joint damage progression.

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Correction notice This article has been corrected since it was published Online First. In table 1 the units for CRP have been corrected to mg/L.

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