SUPPLEMENTARY MATERIALS

Assessments The wrist and hand were scanned separately with surface coils using a positioning frame and biplanar slice alignment to ensure reproducibility. Pulse sequences included coronal 2-dimensional short-tau inversion recovery (STIR) and coronal fat-saturated, T1-weighted 3-dimensional (3D) gradient echo (3D GRE) with and without intravenous gadolinium-based contrast. Voxel dimensions were 469µ x 625µ x 3,000µ for STIR and 203µ x 625µ x 1,500µ for 3D GRE.

MRI images were evaluated at a central reading facility by two independent radiologists using the Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system [1]: synovitis (scale, 0–3 in 8 joints), osteitis (scale, 0–3 in 25 bones) and bone erosion (scale, 0–10 in 25 bones). All time points for an individual patient were viewed simultaneously but in random order and with the dates masked. The scores of the two radiologists were averaged, and the top 5% of discrepancies for total change scores relative to baseline for each RAMRIS feature were adjudicated by consensus review. The interclass correlation coefficients (ICCs) for synovitis, osteitis and erosion were 0.94, 0.96 and 0.91 at baseline, respectively. ICC values for change from baseline to the last time point available for each patient were 0.89, 0.95 and 0.82, respectively.

Statistical analysis

Adjusted mean changes from baseline in magnetic resonance imaging (MRI) scores were calculated at Months 12 and 18 and analysed in the intent-to-treat (ITT) population (all randomised patients who received at least one dose of study medication in the treatment period, with patients analysed according to randomised treatment). If the score for a given parameter (erosion, osteitis or synovitis) was missing for >20% of joints, the MRI score for each parameter was considered missing. A linear mix model was used to handle missing data when a series of outcomes were measured repeatedly over time. Under the Missing At Random (MAR) assumption, the methods above provided an unbiased estimate of the treatment effect that would have been observed if all patients had continued on treatment for the full study duration.

Adjusted mean differences between treatment groups and associated standard errors (SEs) and two-sided 95% confidence intervals (CIs) were also calculated for abatacept plus MTX and abatacept monotherapy versus MTX alone using the same model. Although no formal statistical testing was performed for these secondary MRI efficacy endpoints, p values were calculated.

Response rates were calculated as point estimates with associated 95% CI for treatment difference. The 95% CIs for a response rate within treatment group were based on normal approximation, provided there were at least five events in each treatment group; otherwise, the exact method was used. The 95% CI for treatment difference in response rate was constructed using the continuity correction.

For the proportion of patients achieving DAS-defined remission (DAS28 [CRP] <2.6) and MRI non-progression, missing DAS-defined remission not due to premature discontinuation and not at treatment period Day 1 or withdrawal period Day 169 was imputed as DAS-defined remission if the missing value was between two observed DAS-defined remissions.

Results

A small number of patients who achieved DAS-defined remission at Month 18 still had MRI progression in synovitis, osteitis and erosion, respectively: abatacept plus MTX (0, 0, 1 patients, respectively); abatacept monotherapy (1, 0, 1 patients) and MTX alone (1, 1, 2 patients).

Discussion

MRI assessments following abatacept treatment have previously been reported in the ADJUST trial in MTX-naïve patients with undifferentiated inflammatory arthritis or very early RA, in the ASSET trial in patients with established RA and an inadequate response to MTX and in patients with psoriatic arthritis.[2-4] A notable difference between ASSET and this study was that the low baseline mean synovitis scores in the ASSET cohort (due to the use of wrist synovitis scores alone being included) made it difficult to show a difference in synovitis outcomes.[4] Data from the current analysis show that abatacept does reduce joint inflammation as indicated by osteitis in patients with early RA.

References

1. Ostergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol 2003;30:1385-6.

2. Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum 2011;63:939-48.

3. Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis 2010;69:510-6.

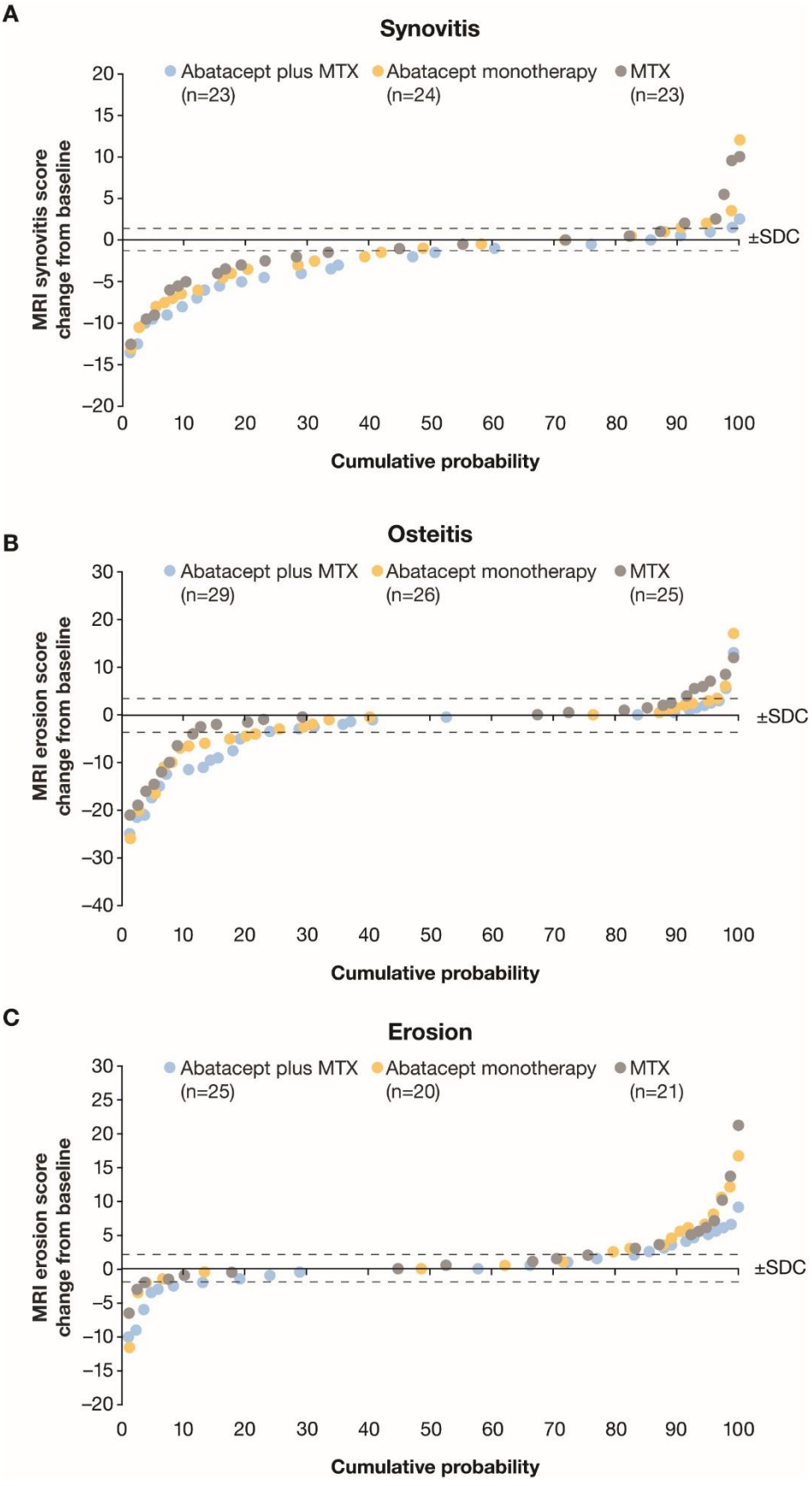
4. Conaghan PG, Durez P, Alten RE, et al. Impact of intravenous abatacept on synovitis, osteitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Ann Rheum Dis 2013;72:1287-94.

Supplementary Table 1 Mean (SE) change in CRP from baseline

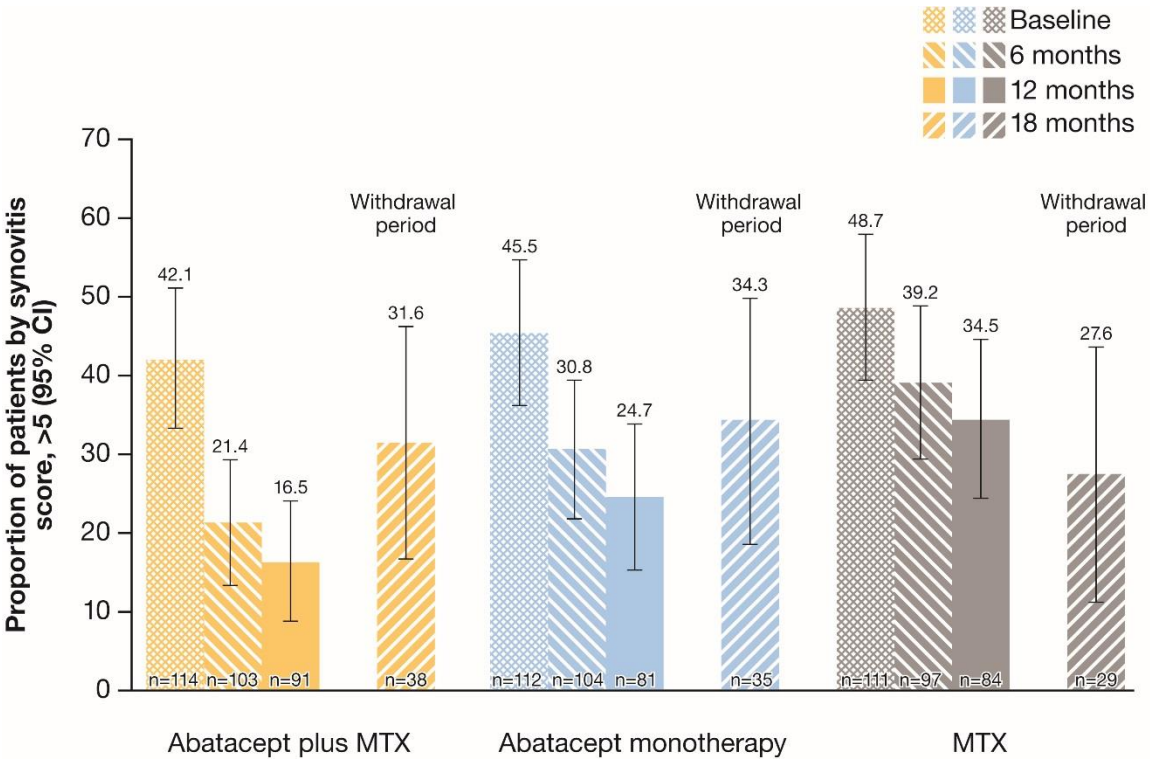
	Abatacept plus MTX (n=119)	**Abatacept monotherapy (n=116)**	**MTX (n=116)**
6 months	–11.99 (2.08) (–16.12, –7.87)	–9.68 (2.84) (–15.31, –4.06)	–9.14 (2.23) (–13.57, –4.72)
12 months	–12.73 (2.24) (–17.18, –8.27)	–11.63 (2.49) (–16.58, –6.68)	–8.01 (2.27) (–12.51, –3.50)
18 months (withdrawal period)	–6.72 (3.06) (–12.87, –0.56)	–2.07 (2.63) (–8.01, 2.62)	–4.37 (4.02) (–12.54, 3.81)

Months 6 and 12 represent study treatment period. 95% confidence intervals are presented.

Supplementary Figure 1 Cumulative probablility plots of change from baseline in MRI scores. Change from baseline in (A) synovitis (B) osteitis (C) erosion scores at Month 12. SDC values were 2.01, 2.81 and 2.29, respectively. MRI, magnetic resonance imaging; SDC, smallest detectable change.


A
Synovitis
Abatacept plus MTX (n=23)
Abatacept monotherapy (n=24)
MTX (n=23)
MRI synovitis score change from baseline
±SDC
Cumulative probability
B
Osteitis
Abatacept plus MTX (n=29)
Abatacept monotherapy (n=26)
MTX (n=25)
MRI erosion score change from baseline
±SDC
Cumulative probability
C
Erosion
Abatacept plus MTX (n=25)
Abatacept monotherapy (n=20)
MTX (n=21)
MRI erosion score change from baseline
±SDC
Cumulative probability

Supplementary Figure 2 Proportion of patients with a synovitis score >5 at 6, 12 and 18 months. Error bars represent 95% CIs. All randomized and treated patients (ITT population) with synovitis score measurement at baseline. The total population is presented; n, includes all patients irrespective of remission status. CI, confidence interval; ITT, intent-to-treat; MTX, methotrexate.



Supplementary Figure 3 Adjusted mean change from baseline in MRI scores; *post hoc* analysis in patients with DAS28 (CRP) <2.6 both at Month 12 and at Month 18. There were no significant differences versus MTX. MRI scores were adjusted for baseline and corticosteroid use at baseline (yes/no). Error bars represent standard errors; n=number of patients who are in remission. CRP, C-reactive protein; DAS, Disease Activity Score; MRI, magnetic resonance imaging; MTX, methotrexate.