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Effects of TOFACITINIB on MRI Endpoints in METHOTREXATE-Naive Early Rheumatoid Arthritis: A Phase 2 MRI Study With Semi-Quantitative and Quantitative Endpoints.

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Background: Inflammation of the synovium and in particular the bone marrow, as assessed by magnetic resonance imaging (MRI), have been identified as prognostic indicators of structural joint damage in patients (pts) with rheumatoid arthritis (RA). Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Inhibition of structural damage has been shown using conventional radiography in pts receiving tofacitinib for moderate to severe RA.[1,2]

Objectives: To explore the effects of tofacitinib, with or without methotrexate (MTX), on a range of sensitive MRI endpoints.

Methods: This was an exploratory, Phase 2, randomised, double-blind, parallel group, multicentre study (A3921068; NCT01164579) in MTX-naive adults with early active RA (duration ≤2 years) and evidence of clinical synovitis in an index wrist or metacarpophalangeal (MCP) joint. Pts were randomised 1:1:1 to receive tofacitinib 10 mg twice daily (BID) + MTX, tofacitinib 10 mg BID + placebo (PBO) or MTX + PBO, for 1 year. MRI endpoints in the wrist and MCP joints were assessed using 3 methods: OMERACT RAMRIS; a novel automated method quantifying RAMRIS components using Active Appearance Modelling (RAMRIQ; Imorphics UK); and dynamic quantitative MRI (Dynamika, UK). Evaluable pts were assessed using a mixed effect model for repeated measures to evaluate endpoints (statistical significance at 10% [2-sided] level). Scoring was performed by one centralised reader blinded to time point and treatment.

Results: Of 109 pts randomised and treated, most were female and Caucasian. Disease duration was consistent with early RA (mean: 0.6–0.8 years). Mean age, disease activity and MRI evaluations were similar across treatment groups at baseline (BL). More pts from the tofacitinib + MTX and tofacitinib + PBO groups completed the study (n=28, n=27, respectively) vs MTX + PBO (n=21). Mean BME improvements, measured with RAMRIS and RAMRIQ only, were statistically greater in both tofacitinib groups vs MTX + PBO at M3, M6 (primary; RAMRIS) and M12. Synovitis improvements were observed in all groups; numerical improvements were observed in both tofacitinib groups vs MTX + PBO with RAMRIS, but statistically significant differences were observed for both tofacitinib groups across time points with the more sensitive RAMRIQ, which was consistent with dynamic MRI findings (Table 1). Significantly less erosive damage was seen using RAMRIS and RAMRIQ in both tofacitinib groups vs MTX + PBO at M6 and M12 (Table 1).

Conclusions: These results provide consistent evidence using 3 different MRI assessment technologies that tofacitinib treatment leads to early reduction of inflammation and lack of progression of structural damage.

Table 1. MRI endpoints (RAMRIS, RAMRIQ and dynamic quantitative MRI)

	Tofacitinib 10 mg BID + MTX (N=36)	Tofacitinib 10 mg BID + PBO (N=36)	MTX + PBO (N=37)
Change from baseline in bone marrow oedema score, LS mean (SE), evaluable set			
RAMRIS			
Month 3	-0.77 (0.42)*	-0.86 (0.41)*	0.47 (0.41)
Month 6 (Primary)	-1.26 (0.41)**	-1.45 (0.42)**	0.29 (0.42)
Month 12	-1.52 (0.42)***	-1.70 (0.43)***	0.59 (0.46)
RAMRIQ			
Month 3	-0.71 (0.45)*	-0.80 (0.44)*	0.61 (0.45)
Month 6	-1.01 (0.45)**	-0.85 (0.46)*	0.82 (0.45)
Month 12	-1.00 (0.46)*	-0.94 (0.47)*	0.29 (0.49)
Change from baseline in synovitis score, LS mean (SE), evaluable set			
RAMRIS			
Month 3 (Primary)	-0.80 (0.41)	-0.69 (0.40)	-0.17 (0.40)
Month 6	-1.22 (0.40)	-1.29 (0.41)*	-0.28 (0.42)
Month 12	-2.26 (0.41)*	-1.16 (0.43)	-0.66 (0.46)
RAMRIQ			
Month 3	-2739 (626.01)**	-1757 (608.53)*	91.86 (637.33)
Month 6	-4062 (607.60)****	-3355 (637.22)***	-239.8 (637.90)
Month 12	-4355 (632.32)***	-3983 (661.67)**	-900.2 (703.38)
Dynamic quantitative MRI (total enhancing voxels)			
Month 3	-1324 (372.76)***	-889.6 (371.28)**	520.67 (383.33)
Month 6	-1526 (358.69)*	-1511 (378.88)*	-184.5 (393.82)
Month 12	-1700 (372.29)***	-1604 (393.13)**	180.61 (417.85)
Change from baseline in erosion score, LS mean (SE), evaluable set			
RAMRIS			
Month 3	-0.12 (0.25)	0.36 (0.24)	0.44 (0.25)
Month 6	-0.06 (0.25)*	-0.02 (0.25)*	0.65 (0.25)
Month 12	-0.11 (0.25)***	-0.08 (0.25)***	1.18 (0.26)
RAMRIQ			
Month 3	-0.06 (0.10)	-0.10 (0.10)	0.05 (0.10)
Month 6	-0.17 (0.10)*	-0.18 (0.10)*	0.19 (0.10)
Month 12	-0.26 (0.10)*	-0.28 (0.10)*	0.09 (0.11)
Safety events, n (%)			
Patients with AEs (any cause)	25 (69.4)	31 (86.1)	30 (81.1)
Serious AEs	2 (5.6)	1 (2.8)	2 (5.4)
Severe AEs	4 (11.1)	4 (11.1)	1 (2.7)

Evaluable set includes patients who were randomised, received ≥1 dose of study medication, and had endpoint values at both baseline and the time point assessed. The number of evaluable patients in each group varied according to time point and assessment type (range: 19–33).
Mixed effect model for repeated measures: *p<0.1; **p<0.01; ***p<0.001, ****p<0.0001 vs MTX + PBO.

Table 1 - Change in quantitative and RAMRIS measures. chi-sq = Chi-square; ln = natural logarithm; LR = likelihood ratio test; sqrt = square root. *Random slopes model compared to unconditional means model

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[1] Lee EB et al. N Engl J Med 2014; 370:2377-86.

[2] van der Heijde, et al. Arthritis Rheum 2013; 65:559-70.

