THU0175 INFLAMMATION DETECTED WITH MODERN SENSITIVE MRI ANALYSIS DEMONSTRATES THAT THERAPEUTIC RESPONSE AS EARLY AS ONE MONTH PREDICTS 12-MONTH RADIOGRAPHIC PROGRESSION: DATA FROM A STUDY USING TOFACITINIB AND METHOTREXATE IN METHOTREXATE-NAÏVE PATIENTS WITH EARLY RA

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Background: Tofacitinib is an oral JAK inhibitor for the treatment of RA. A novel automated quantification method for RA MRI-detected pathology using statistical shape modelling technology (RAMRIQ) provides a tool that may be even more responsive than the sensitive RAMRIS semi-quantitative standard.[1]
Objectives: To determine if early changes in RAMRIQ were predictive of subsequent MRI and radiographic damage progression in a study of tofacitinib for the treatment of early RA in methotrexate-naïve patients with minimal radiographic progression.
Methods: We used data from an exploratory, Phase 2 randomised controlled trial comparing tofacitinib, methotrexate and the combination (n=109) in methotrexate-naïve patients with early active RA.[1] All patients met ACR classification criteria for active RA. MRI was performed at baseline and at 1, 3, 6 and 12 months. A single centralised reader read all MRI data; data for each patient were randomised by time point and read in the same sitting. We examined changes in synovitis, osteitis and erosions for RAMRIQ and RAMRIS at 1 and 3 months and performed univariate analyses on their relationship to RAMRIS, RAMRIQ and radiographic progression (modified Total Sharp Score [mTSS]) at 12 months.
Results: Reduction in RAMRIQ synovitis and osteitis at 1 and 3 months were significantly associated with reduction in RAMRIS erosion progression at 12 months (Table). Improvement in RAMRIQ synovitis and osteitis at 1 and 3 months were also associated with reduction in radiographic progression at 12 months, while RAMRIQ erosions at 1 and 3 months were not significantly associated with radiographic progression (Table). Early changes in RAMRIS erosion at 1 and 3 months were associated with radiographic progression at 12 months (Table). Treatment with tofacitinib alone or in combination with methotrexate was also associated with reduced progression in RAMRIS erosions (p=0.017 and p=0.007, respectively).

Table. Univariate analyses of the relationship between RAMRIQ and RAMRIS measurements at Month 1 and 3 and RAMRIS erosion and radiographic progression at Month 12.

p value	RAMRIS erosion progression (Month 12)	Radiographic progression (mTSS; Month 12)
Change in RAMRIQ synovitis		
Month 1	0.004	<0.001
Month 3	0.008	0.008
Change in RAMRIQ osteitis		
Month 1	0.001	<0.001
Month 3	<0.001	<0.001
Change in RAMRIQ erosions		
Month 1	-	0.075
Month 3	-	0.530
Change in RAMRIS erosions		
Month 1	-	0.001
Month 3	-	0.005

mTSS, modified Total Sharp Score; RAMRIQ, quantitative RAMRIS; RAMRIS, Rheumatoid Arthritis MRI Scoring System

Conclusions: In this study, sensitive automated detection demonstrated that change in synovitis and osteitis predict subsequent RAMRIS erosion and radiographic progression. Treatment with tofacitinib as monotherapy or in combination with methotrexate was also highly predictive of no progression of erosive damage. Because of its enhanced sensitivity, novel quantitative imaging analysis has the potential to change RA clinical trial design where assessing structural damage is an objective.
References:
[1] Conaghan PG et al. Ann Rheum Dis 2016; 75: 1024–1033.
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THU0176 EFFICIENCY AND SAFETY OF RAPAMYCIN COMBINED WITH LOW-DOSE IL-2 TREATMENT COMPARED WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: The molecular target rapamycin (mTOR) signaling can regulate between effector and regulatory T cell lineage commitment [1]. Rapamycin, the inhibitor of mTOR, has appeared to be a new therapy for several autoimmune diseases, such as systemic lupus erythematosus [2].
Objectives: To evaluate whether rapamycin is beneficial in patients with Rheumatoid Arthritis (RA), and compared with Methotrexate in efficiency and safety.
Methods: Fifty-eight DMARDs-naive RA patients were enrolled, thirty-eight were treated with Rapamycin (0.5 mg every 2 days, combined with IL-2 50WIU per day for 5 days), the others with Methotrexate (10mg per week) taken as control. Clinical improvement and immunological assessments were performed at baseline, 1 and 12 weeks. Treatment group assessed CD4+ T cell subsets by flow cytometry at baseline, 1 and 12 weeks.
Results: We enrolled 58 patients. At baseline, patients had a mean DAS28 of 3.34 (0.81). Rapamycin group and Methotrexate group included 38 and 20 patients, respectively, with no significant differences in baseline characteristics. At 1 week, the mean DAS28 after Rapamycin treatment (2.43 [0.77]) and Methotrexate (2.25 [0.86]) was not significantly different (P=0.43). Same as ESR (24.74 [24.53], 21.76 [24.27], P=0.66). The dose of glucocorticoid during hospitalization of rapamycin treatment group (720.8 [554.3]) was lower than Methotrexate (1202.3 [943.1], P=0.042). The length of hospital stay of Rapamycin (14.5 [3.9]) was lower than Methotrexate (21.0 [3.8], P<0.001). Rapamycin administration resulted in an increase in the absolute counts of Treg cells from a median of 36.82 cell/ul (at week 0) to 99.80 cell/ul (at week 1) (P<0.001). The ratios of Th17/Treg cells showed a reduction from a median of 0.16 to 0.09, and the difference was significant (P=0.047). At 12 week, 5 patients treated with Rapamycin dropped out because of non-compliance. the mean DAS28 was not significantly different (2.36 [0.97], 2.16 [0.86], P=0.51). The same as the daily dose of glucocorticoid (10.21 [32.3], 9.16 [40.1], P=0.804). The absolute counts of Treg cells increased from a median of 36.82 cell/ul (at baseline) to 43.26 cell/ul after Rapamycin administration (P=0.028). The ratios of Th17/Treg had no significant difference from a median of 0.16 at baseline to 0.12 at week 12 (P=0.937). Liver enzyme elevations occurred on 2 patients after Methotrexate therapy for 1 week. However, there were no serious adverse events observed during the 12-week period of rapamycin treatment.
Conclusions: Rapamycin combined with the low-dose IL-2 appears to be a safe and effective therapy for RA, by a rapid increase of circulating Treg cells and a correction of the ratio of Th17/Treg cells, which has gotten a same response compared with Methotrexate.
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THU0177 ABT-494 PHARMACOKINETICS FOLLOWING ADMINISTRATION OF THE ONCE-DAILY EXTENDED-RELEASE TABLET FORMULATION BEING UTILIZED IN THE ONGOING RHEUMATOID ARTHRITIS PHASE 3 TRIALS

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Background: ABT-494 is a selective Janus Kinase 1 inhibitor. In two Phase 2b studies in subjects with rheumatoid arthritis, 6 mg and 12 mg twice-daily (BID) doses of ABT-494 immediate-release formulation achieved optimal benefit-risk profiles. To enhance patients' compliance, an extended-release formulation was developed targeting to achieve comparable exposures with the 6 mg and 12 mg BID of the immediate-release formulation with once-daily (QD) administration.