Figure. Development of prediction model for maximum MTX dose without hepatotoxicity

ROC analysis for total MTXPG concentration discriminating patients with and without hepatotoxicity

Genetic and Clinical model to speculate MTXPG levels

$$\text{MTXPG concentration} = 96 + 7.7 \cdot \text{MTX}(\text{mg}) - 1.7 \cdot \text{BMI} - 28 \cdot \text{RBC} + 120 \cdot \text{creatinine} + 19.3 \cdot \text{GGH}(\text{C/T})$$

$$\text{MTX dose (mg)} = \{100 (\text{MTXPG}) - 96 + 1.7 \cdot \text{BMI} + 28 \cdot \text{RBC} - 120 \cdot \text{creatinine} - 19.3 \cdot \text{GGH}(\text{C/T})\} / 7.7$$

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FRI0130

A SYSTEMATIC REVIEW OF NATURAL SUPPLEMENTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune condition affecting almost 1% of the general population (1). Pharmacological management has been the mainstay of treatment for RA and includes DMARDs and biologics. Despite these therapies, anywhere from 28-90% of patients with RA use complementary and alternative medicine (2). These non-pharmacological therapies range from dietary interventions to supplements to nonprescription therapies.

Objectives: To determine the efficacy of non-pharmacological, orally-ingested interventions on clinically-relevant endpoints in patients with rheumatoid arthritis.

Methods: We systematically reviewed EMBASE and MEDLINE electronic databases from inception until Feb 23, 2019 for relevant articles. Only randomized controlled trials (RCTs) which assessed oral, non-pharmacological interventions (e.g. diets, vitamins, oils, herbal remedies, fatty acids, supplements, etc.) in adult patients with RA, that presented clinically-relevant outcomes (defined as pain, fatigue, disability, joint counts, and/or disease indices) were included.

Clinical outcome data was extracted by two independent authors as difference from baseline measurement. Therapies with at least 3 RCTs which presented data on the same clinical outcome were meta-analyzed using a pooled random effects model using RevMan 5.

Results: A total of 4423 unique articles were independently assessed by two authors, of which 72 articles met our inclusion criteria. Thirteen different interventions were studied more than once, and six interventions had clinical outcomes reported in at least 3 trials. However, only vitamin D and fatty acids met criteria for meta-analysis.

Pooled random effects models suggested vitamin D supplementation improved HAQ scores from baseline (mean difference = -0.10, 95% confidence interval (CI) = -0.17 to -0.02; p=0.01) but had no effect on DAS28 scores (Table 1).

Table 1. Mean differences from baseline of various clinical outcomes in RA patients taking vitamin D or fatty acid supplementation compared to control group.

Clinical Outcome	Total Patients	Mean Difference (95% CI)	P-value
Vitamin D			
HAQ	573	-0.10 (-0.17 to -0.02)	0.01
DAS28	174	-0.30 (-0.71 to 0.11)	0.15
Fatty Acids			
TJC	661	-2.05 (-2.83 to -1.27)	0.04
SJC	582	-0.35 (-0.96 to 0.26)	0.26
RAI	234	-1.82 (-4.69 to 1.05)	0.21
Pain	756	-0.61 (-1.02 to -0.20)	0.004
Patient Global	484	-0.26 (-0.59 to 0.07)	0.12
Physician Global	382	-1.08 (-1.98 to -0.18)	0.02
HAQ	277	-0.13 (-0.18 to -0.09)	<0.001
DAS28	543	-0.19 (-0.36 to -0.01)	0.03

Fatty acid supplementation improved total joint counts, pain, physician global assessment scores, HAQ, and DAS28 from baseline (Table 1). There were significantly more patients who achieved ACR20 criteria (Relative Risk Ratio = 2.73, 95% CI 1.62-4.58; p<0.001) (Figure 1).

<https://account-congress.eular.org/Modules/Abstract/Submission/summary.aspx>

Figure 1. Forest plot of studies in which RA patients taking fatty acids achieved ACR20 criteria. <https://account-congress.eular.org/Modules/Abstract/Submission/summary.aspx>

Conclusion: From our meta-analysis, vitamin D and fatty acids supplementation showed statistically significant improvement in some clinical outcomes in patients with RA; however, the degree of improvement is unlikely to be clinically significant. Overall, many trials were of low quality and had high risks of bias including inadequate reporting of data. Further clinical trials that are well-designed and fully powered are still needed to confirm the efficacy of many supplements and diets in RA.

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FRI0131

SUSTAINABILITY OF RESPONSE BETWEEN UPADACITINIB AND ADALIMUMAB AMONG PATIENTS WITH RHEUMATOID ARTHRITIS AND PRIOR INADEQUATE RESPONSE TO METHOTREXATE

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Background: The primary treatment goal for patients (pts) with rheumatoid arthritis (RA) is a state of sustained clinical remission (REM) or low disease activity (LDA).^{1,2}

Objectives: To assess the long-term sustainability of response to upadacitinib (UPA), a JAK inhibitor, and adalimumab (ADA), both with background methotrexate (MTX), among pts with RA and prior inadequate response to MTX.

Methods: In the phase 3, randomized, placebo (PBO) and active-controlled SELECT-COMPARE trial, pts on stable background MTX received UPA 15 mg once daily, PBO, or ADA 40 mg every other week. Pts not achieving 20% improvements in tender/swollen joint counts (Weeks 14-22) or LDA (CDAI ≤ 10 at Week 26) were rescued from UPA to ADA or PBO/ADA to UPA; all non-rescued PBO pts were switched to UPA at Week 26. This post hoc analysis evaluated clinical REM (CDAI ≤ 2.8 ; SDAI ≤ 3.3), LDA (CDAI ≤ 10 ; SDAI ≤ 11), and DAS28(CRP) $< 2.6/\leq 3.2$ at first occurrence before Week 72 or prior to treatment switch; additionally, these measures were evaluated at 3, 6, and 12 months after the first occurrence for the total number of pts randomized to UPA (n=651) or ADA (n=327). Sustainability of response was evaluated by Kaplan-Meier only for those pts who achieved REM/LDA and was defined as time to the earliest date of losing response at two consecutive visits, discontinuation of study drug, or losing response at the time of rescue. The predictive ability of time to clinical REM/LDA was assessed using Harrell's concordance (c)-index (for reference, an index ~ 0.5 , indicates no ability to predict; an index of 1 or -1 would be a perfect prediction). The date of the last follow up was 6 July, 2018, when all pts had reached the Week 72 visit.

Results: Through Week 72, a significantly higher proportion of pts receiving UPA + MTX vs ADA + MTX achieved CDAI REM (41% vs 31%, p=.0035) as well as CDAI LDA (70% vs 59%, p=.0007). 26%/22% of pts randomized to UPA + MTX and 16%/14% of pts randomized to ADA + MTX achieved sustained CDAI REM at 6/12 months after the first occurrence. Additionally, 49%/46% of pts randomized to UPA + MTX and 36%/34% of pts randomized to ADA + MTX achieved sustained CDAI LDA at 6/12 months after the first occurrence (Figure 1). Time to initial clinical REM/LDA did not appear to be associated with sustained disease control. The c-indices (95% CI) for CDAI REM in the UPA + MTX and ADA + MTX groups were 0.528 (0.48, 0.58) and 0.510 (0.43, 0.59) and that of LDA were 0.601 (0.56, 0.64) and 0.555 (0.50, 0.61), respectively. Through last follow-up visit, 51% of UPA + MTX pts and 45% of ADA + MTX pts remained in CDAI REM while 65% of UPA + MTX pts and 58% of ADA + MTX pts remained in CDAI LDA, respectively (Figure 2). Similar results were observed across other disease activity measures (SDAI REM/LDA and DAS28(CRP) $< 2.6/\leq 3.2$).

Conclusion: A significantly greater proportion of pts with RA and prior inadequate response to MTX receiving UPA + MTX vs ADA + MTX achieved clinical REM or LDA across disease activity measures. REM and LDA were sustained through Week 72 in both treatment arms, with numerically higher proportions retaining response among UPA-treated pts.

References:

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Figure 1. Proportion of patients sustaining CDAI remission or low disease activity at 3, 6, and 12 months after the first occurrence of response among the total randomized population

UPA, upadacitinib; ADA, adalimumab; MTX, methotrexate; QD, once daily; EOW, every other week; CDAI, Clinical Disease Activity Index; n, total number of patients randomized to UPA or ADA.

Data for patients who maintained response through the cut-off (6 July 2018, when all patients had reached Week 72 visit) were assessed. Non-responder imputation was used for missing data.

Figure 2. Kaplan-Meier analysis of time to loss of CDAI remission or low disease activity after the first occurrence of response

UPA, upadacitinib; ADA, adalimumab; MTX, methotrexate; QD, once daily; EOW, every other week; CDAI, Clinical Disease Activity Index; n, number of patients who had achieved CDAI remission or low disease activity.

Results are for patients who had achieved CDAI remission or low disease activity. UPA 15 mg QD + MTX: CDAI ≤ 2.8 n = 267; CDAI ≤ 10 n = 496. ADA 40 mg EOW + MTX: CDAI ≤ 2.8 n = 102; CDAI ≤ 10 n = 193.

Data for patients who maintained response through the cut-off (6 July 2018, when all patients had reached Week 72 visit) were assessed. Non-responder imputation was used for missing data. Week 0 indicates the first occurrence of response.

Disclosure of Interests:

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FRI0132 EFFICACY AND SAFETY OF SWITCHING JAKINIBS IN RHEUMATOID ARTHRITIS

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Background: Different Jakinibs (JAKi) have shown efficacy in rheumatoid arthritis (RA) but in an important proportion of patients, insufficient response leads to therapy withdrawal. The different JAKi show variable selectivity for the four Jak isoforms (Jak1,2,3 y Tyk2) but there are no clinical trials analyzing the response to a JAKi after the suspension of another JAKi and therefore, observational data may be useful in this regard.

Objectives: To describe efficacy and safety of the second JAKi in patients with suspension of the first due to failure or side effects.

Methods: Spanish observational multicentric study. Data were retrospectively obtained from medical records of 28 patients with RA sequentially treated with baricitinib or tofacitinib in any order.

Results: We identified 28 patients with RA treated with baricitinib and tofacitinib. Patient's characteristics are summarized in Table 1. Half of the patients received tofacitinib first, and the other half baricitinib as the first JAKi. Mean survival for the first JAKi was 7,6 $\pm$ 6,1 months. The reason for withdrawal was inefficacy in 17 cases (61%) and adverse effects in 11 (39%). Mean follow-up after starting on the second JAKi was 9,6 $\pm$ 5,6 [3-19] months. Disease activity data along follow-up are depicted in Table 2. Survival on the second JAKi was 82% at 3, 76% at 6, and 62% at 12 months when 13 of the 21 patients maintained the therapy. In all 8 patients who discontinued the second JAKi, the reason was inefficacy. The treatment suspension rate was similar among patients discontinuing the first JAKi for inefficacy (n=5, 29,4%) or for adverse effects (n=3; 27,3%).

Table1. Baseline Characteristics.

	N 28
Clinical characteristics	
Female	24 (86%)
Age*	61,2 $\pm$ 13,2
ACPA (+)	19 (67,9%)
Erosions	13 (46,4%)
Extra-articular manifestations	8 (28,6%)
TJC*	10,8 $\pm$ 5,4
SJC *	7,4 $\pm$ 4,6
DAS28-CPR*	5,4 $\pm$ 0,91
High disease activity	71,5%
Moderate disease activity	23,8%
Low disease activity	4,7%
Previous treatment	
bDMARD	24 (86%)
Nº of previous bDMARDs *	3,9 $\pm$ 2,2
ITNF	75%
No-ITNF	67,9%

(*) Mean $\pm$ SD