Table 2. Genes expressed abnormally in PBMCs of TAK patients

	Abnormally expressed in untreated TAK		Abnormally expressed in treated TAK		Influenced by treatment		Associated with the TAK activity	
	upregulated	downregulated	upregulated	downregulated	upregulated	downregulated	Upregulated	downregulated
Genes associated with the TLRs-NFκB pathway	<i>TLR2, TLR4, p50, p65, IκBα, CTLA4</i>	—	<i>TLR2, TLR4, IκBα</i>	—	—	<i>p50, p65</i>	<i>p50</i>	—
Positive and negative costimulatory molecules and their ligands	—	<i>CD40</i>	<i>PD-1</i>	<i>CD40, LAG3</i>	—	<i>CD28, CTLA4</i>	<i>CD28</i>	—
Genes associated with the activation or differentiation of T cell or B cell	<i>CD3, BCL6</i>	—	<i>BCL6</i>	<i>TCR</i>	—	<i>CD3, TCR, RORC</i>	<i>TCR, GATA3, RORC, FOXP3</i>	—

Figure 1. mRNA abundance of genes in PBMCs of TAK patients analyzed by qPCR. (a)–(e) Partial genes associated with TLRs-NFκB pathway. (f)–(l) Partial genes associated with the TLRs-NFκB pathway or costimulatory molecules. (m)–(p) Partial genes associated with the activation or differentiation of T cell or B cell. (a)–(f) Compare the untreated TAK group with the HC group whose data normalized to one. (b)–(g) Compare the treated TAK group with the HC group whose data normalized to one. (c)–(h) Compare the untreated TAK group with the treated TAK group whose data normalized to one. (d)–(i) Compare the active untreated TAK group with the nonactive treated TAK group whose data normalized to one. (e)–(j)–(p) Pearson correlation test, n=27 (all TAK patients enrolled). (q)–(s) Spearman correlation test, n=27 (all TAK patients enrolled). Data are mean ± SEM. Untreated TAK group, n=7. Treated TAK group, n=20. Active untreated TAK group, n=9. Nonactive treated TAK group, n=11. HC group, n=11. *, P<0.05. **, P<0.01. ***, P<0.001. ****, P<0.0001.

Figure 2. Correlation between any two genes expressed abnormally in PBMCs of TAK patients. Cluster Analysis by the result of Spearman correlation test. n=27 (all TAK patients enrolled).

Conclusion: TLRs-NFκB pathway may be activated in TAK patients, with upregulation of *BCL6*, and there may be deficiency of *CD40*. *TLR2*, *TLR4*, *PD-1*, *LAG3*, *CD40* and *BCL6* may play roles in the pathogenesis of TAK. *p50*, *CD28*, *TCR*, *GATA3*, *RORC* and *FOXP3* may be related to the disease activity of TAK.

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Rheumatoid arthritis - prognosis, predictors and outcome

FRI0018

USING SELF-REPORTED OUTCOMES TO DETECT NEW-ONSET FLARE IN A REAL-WORLD STUDY OF PARTICIPANTS WITH RHEUMATOID ARTHRITIS - INTERIM RESULTS FROM THE DIGITAL TRACKING OF ARTHRITIS LONGITUDINALLY (DIGITAL) STUDY

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Background: Patients with rheumatoid arthritis (RA) experience fluctuating symptoms, increased pain, decreased function and variable quality of life; such changes often occur between visits to clinicians. Digital Tracking of Arthritis Longitudinally (DIGITAL) study² is evaluating the use of electronically captured patient-reported outcomes (ePRO) and passive data collection from a Fitbit device to identify disease worsening in a real-world study of participants (pts) with RA.

Objectives: Evaluate agreement between self-reported new-onset flare and ePROs in an interim analysis from DIGITAL using a classification model.

Methods: Members of the ArthritisPower registry with RA were invited to participate in DIGITAL. Pts who successfully completed a two-week Lead-in period entered the Main Study in which they wore a smartwatch and provided daily (pain and fatigue numeric rating scales (NRS)) and weekly ePROs, including the OMERACT RA Flare Questionnaire (FLARE) and PROMIS measures. This interim analysis is of ePRO data from pts who completed at least 30 days of the Main Study. A "Yes" response to the FLARE item, "Are you having a flare now?" identified flare. For modeling association between new-onset flare and ePRO, the dataset was split into training (the first 30 days of the Main Study) and test data (Day 31 and following). Within each dataset, repeated binary outcomes (Flare/No Flare) per pt were defined each week. To focus on new-onset flare, within each dataset, outcomes for patient weeks for which flare was present in the previous week were excluded.

Candidate variables for the model included baseline and current FLARE score (0-50 scale) and each of its 5 items, daily pain, daily fatigue, and several PROMIS weekly instruments and their lagged values (last week or last 6 days for daily). 'Baseline' was calculated in non-flare weeks. Training data was used for logistic regression model selection combining clinical expertise with backward elimination. Performance of the final model was evaluated using test data.

Results: The training data was composed of outcomes from 128 pts who reported 388 weekly flare assessments as no flare or onset flare over 2800 days during the first month of the Main Study. Of pts in the training dataset, 92.2% were female, 87.5% white, with mean age (SD) 52.7 (11.0) and years since RA diagnosis 10.4 (10.3); 62.5% were on a biologic. Among those in the training dataset, 58 flare outcomes occurred in 50 (39.1%) unique pts.

The test data comprised outcomes from 123 pts who reported 442 weekly flare assessments as no flare or onset flare over 3366 days in which 64 flare outcomes occurred, and primarily included continued observations from pts who contributed to the training dataset.

The best-performing model to classify flare in training data included the current and baseline FLARE instrument activity question (i.e. "Considering how active your rheumatoid arthritis has been, how much difficulty have you had when taking part in activities such as work, family life, social events that are typical for you during the last week"), current daily pain, and baseline daily pain average and standard deviation. In test data, this model had an area under the receiver operator curve of 0.81 (Figure). At a cut point requiring specificity to be ≥0.80, sensitivity to detect flare was 0.62 and overall accuracy was 0.78.

Conclusion: New-onset flare is common among RA patients, and the FLARE instrument and daily pain scores appear effective to classify it. Evaluation of passive data as a proxy for self-reported new-onset flare is ongoing.

References:

- [1] Bartlett SJ, et al. *JRheumatol*, 2017;44:1536-43.
[2] Nowell WB, et al. *JMIR Res Protoc*, 2019;8:e14665.

Figure. Performance of Flare Classification Using Best Fit Model*

*Model using current and prior week single-item for "difficulty taking part in work, family life and social events" from the FLARE instrument, and current daily pain and baseline daily pain average and standard deviation.

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FRI0019

MRI INFLAMMATION, DISEASE ACTIVITY AND FUNCTIONAL IMPAIRMENT ARE MORE EFFECTIVELY REDUCED BY ESCALATION TO BIOLOGICS COMPARED TO csDMARD-ESCALATION IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION FOLLOWING A TREAT-TO-TARGET STRATEGY: SECONDARY ANALYSES OF THE IMAGINE-RA TRIAL

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Background: The effect of different treatment escalations on MRI inflammation in rheumatoid arthritis (RA) patients following an MRI treat-to-target (T2T) strategy has not previously been investigated.

Objectives: To compare the effect of different treatment escalations on MRI inflammation, physical function and disease activity in RA patients in clinical remission, following an MRI T2T strategy.

Methods: One hundred RA patients in clinical remission (DAS28-CRP < 3.2 and no swollen joints), on conventional synthetic (cs) DMARDs following an MRI T2T strategy targeting DAS28-CRP ≤ 3.2, no swollen joints plus absence of MRI osteitis, were followed for 2 years with clinical and MRI (wrist and 2nd-5th MCP joints) evaluation every 4 months¹. If target was not met, a predefined treatment escalation algorithm dictated: First: increase in csDMARDs (A), second: adding a TNF inhibitor (TNFi) (B), third and onwards: switch between biologics (C). If target was met, no change in baseline csDMARDs was done (D). Outcomes were assessed 4 months after treatment change. MRIs were evaluated with known chronology by one experienced reader. Repeated measures mixed linear models were used to express estimates of group differences on predefined co-primary outcomes (MRI osteitis, HAQ) and key secondary outcomes (MRI combined inflammation, Simplified Disease Activity Index (SDAI)).

Results: Escalation to first TNFi (B) or to 2nd or later biologic (C) compared to csDMARDs (A) was consistently more effective on all outcomes (e.g. in group B osteitis was reduced with 1.8 units more than A) (Table). Unchanged (D) compared to escalation in csDMARD (A) treatment did not differ, except for HAQ-score. Escalation to a 2nd or later biologics (C) compared to the first TNFi (B) was more effective suppressing MRI inflammation. Escalation to TNFi treatment (B) or to 2nd or later biologic (C) compared to unchanged treatment (D) was more effective on all outcomes except from HAQ-score (no difference between groups).

Conclusion: T2T-based treatment escalations to biologics compared to csDMARD-escalations more effectively improved MRI inflammation, physical function and disease activity. Further optimization of the treatment in RA patients in clinical remission may improve long-term outcomes.

References:

- [1] Møller-Bisgaard et al. *JAMA* 2019

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Comparisons of treatment escalations¹

A: Increment in csDMARD mono/combination therapy (n=73); B: Switch from csDMARD combination therapy to TNFi (n=39); C: Switch from TNFi to 2nd biologic/switch between biologics (n=21); D: No change in csDMARDs from baseline (n=58)

	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Outcomes						
Primary						
MRI	1.8 (1.0; 2.6) p<.0001	3.6 (2.3; 4.8) p<.0001	0.3 (-0.3; 1.0) p=.32	1.8 (0.8; 2.9) p=.0006	-1.4 (-2.4; -0.5) p=.0045	-3.3 (-4.6; -1.9) p<.0001
Osteitis			0.054			-0.037
HAQ	0.081 (0.033; 0.13) p=.0011	0.091 (0.031; 0.15) p=.0032	(0.014; 0.095) p=.0091	0.0092 (-0.051; 0.070) p=.77	-0.027 (-0.082; 0.028) p=.33	(-0.10; 0.031) p=.29
Key secondary						
MRI combined inflammation ^a	2.5 (0.9; 4.1) p=.0018	5.4 (3.1; 7.7) p<.0001	0.4 (-0.9; 1.8) p=.52	2.9 (0.8; 4.9) p=.0064	-2.1 (-4.0; -0.2) p=.032	-5.0 (-7.5; -2.4) p=.0002
SDAI	2.7 (1.9; 3.5) p<.0001	2.4 (1.4; 3.4) p<.0001	0.5 (-0.2; 1.2) p=.14	-0.3 (-1.3; 0.7) p=.60	-2.2 (-3.1; -1.3) p<.0001	-1.9 (-3.0; 0.8) p=.0006

¹ Estimates of group differences (least squares means (95% CI)).

^a Sum score of synovitis, osteitis and tenosynovitis