Research letter: Sirukumab and adalimumab reduce power Doppler ultrasound signal in rheumatoid arthritis patients by 4 weeks in a phase 3 trial.

Kristen Sweet,[1] Bidisha Dasgupta,[1] Dick de Vries,[2] Benjamin Hsu,[1] Ian Gourley,[1] Matthew J. Loza,[1] Peter C. Taylor[3]

[1]Janssen Research & Development, LLC, Spring House, PA, United States; [2]Janssen Biologics B.V., Leiden, The Netherlands; [3]Botnar Research Centre, University of Oxford, Oxford, United Kingdom.

Corresponding author:

Peter C. Taylor MA, PhD, FRCP., Botnar Research Centre, University of Oxford, Oxford, OX3 7LD, United Kingdom. Email: peter.taylor@kennedy.ox.ac.uk, Tel: 01865 227323

Clinical trials in RA involve assessment of response by endpoints including composite measures of disease activity. However, many of the components are subjective and insensitive to change and their use in phase 3 studies necessitates large and costly trials.

In single-, or two-centre RA studies, Greyscale US (GSUS) and power Doppler US (PDUS) imaging of a limited joint set is an early and reliable indicator of therapeutic response.[1-3] However, use of ultrasound (US) endpoints in multi-centre clinical trials presents challenges of operator-dependency and variability in image acquisition, even when using the same model and settings of US machine.

We undertook an exploratory multicenter, US substudy, nested within the SIRROUND-H trial[4], to evaluate effects of sirukumab and adalimumab on synovial thickness and vascularity by GSUS and PDUS respectively in 41 consenting subjects (supplementary Table S1) at 9 clinical sites. At each site, ultrasonographers blinded to treatment assessed 12 joints (10 metacarpophalangeal [MCP] joints plus wrists) at Weeks 0, 2, 4, 8, and 24. The same model LOGIQ S8 RD US machine with an ML6-15 probe was used at each site. Scan Assistant, Compare Assist, LOGIQ S8 RD Flow Quantification Option and LOGIQView software were used to analyze images.

Synovial vascularity and thickness were determined by the average scores of 2 independent central readers on a semi-quantitative scale from 0-4 for each joint[2], with adjudication by a third reader if needed.

Wilcoxon signed-rank and Mann-Whitney tests were used to test significant differences ($p<0.05$) between baseline and subsequent timepoints. Pearson correlation was used to test associations between PDUS and clinical variables (significance defined as $p<0.05$ and correlation coefficient $r>0.3$).

Participants were enrolled from 5 countries including 27 subjects randomized to sirukumab and 14 to adalimumab.

Vascularity and thickness scores were highly correlated between readers (vascularity: $p<0.0001$, $r=0.84$; thickness: $p<0.0001$, $r=0.85$). Median (IQR) vascularity scores across all reads were 3 (0-9) and 3 (0-10) for the two readers. The median (IQR) of the standard deviations of repeated reads were 1.1 (0-2.1) and 0.7 (0-2.1) for intra-reader variability of vascularity score, and 1.4 (0-2.8) for inter-reader variability.

Both baseline vascularity and thickness scores were positively associated with RF ($p<0.05$) and ACPA seropositivity ($p<0.05$). Additionally, vascularity ($r=0.35$-0.65) and thickness ($r=0.51$-0.72) were significantly correlated with baseline disease activity measured by DAS28-CRP, DAS28-ESR, CDAI, swollen and tender joint counts (28 joints and only MCP/wrist joints) ($p<0.05$; Table 1).

To our surprise, 15/41 subjects had a baseline vascularity score <1, negating the possibility for evaluable improvement. There was no significant difference in clinical response between subjects with or without a baseline vascularity signal. Only subjects with baseline

vascularity score $\geq$ 1 were evaluated for post-baseline analyses (n=26). In these, PDUS was significantly reduced by both sirukumab (n=19) and adalimumab (n=7) as early as Week 4, and sustained through Week 24 (Figure 1a). There was no significant difference in vascularity change between treatments. In contrast, synovial thickness was only significantly changed from baseline in the sirukumab group at Weeks 4 and 24. (Figure 1b).

At Wk24, for combined treatment groups, PDUS change did not significantly correlate with clinical activity change (Wk24 minus baseline) by any measure ($p>0.05$) consistent with previous reports.[5,6] In contrast, at Wk24, GSUS change correlated with changes in all clinical activity scores evaluated ($r=0.40$-0.59) except DAS28-CRP. DAS28-CRP remission at Wk24 was associated with lower baseline vascularity and thickness scores (median(IQR) 0(0,0) and 1(.25,2.25) respectively; 4/41 subjects achieved DAS-CRP remission at Wk24: vascularity $p=0.0077$; thickness $p=0.0107$) for subjects treated with either sirukumab or adalimumab.

In conclusion, our study demonstrated that US helps to detect improvement early; changes in clinical findings do not correlate with PDUS; patients with lower PDUS at baseline more commonly achieve remission.

Figure 1.

Table 1: Relationships between joint vascularity and thickness and baseline and week 24 changes in disease activity and joint counts

Correlation coefficient (p-value)	Baseline scores [a]		Week 24 change from baseline [b]	
	Vascularity	Thickness	Vascularity	Thickness
CDAI	0.50 (0.0009)[c]	0.67 (<0.0001)	-0.01 (0.9491)	0.40 (0.0170)
DAS28(CRP)	0.65 (<0.0001)	0.72 (<0.0001)	-0.13 (0.5424)	0.27 (0.1126)
DAS28(ESR)	0.53 (0.0005)	0.62 (<0.0001)	-0.03 (0.8815)	0.59 (0.0002)
Swollen joints count (28 joints)	0.35 (0.0268)	0.51 (0.0007)	0.01 (0.9537)	0.52 (0.0011)
Tender joints count (28 joints)	0.44 (0.0043)	0.57 (0.0001)	0.02 (0.9224)	0.55 (0.0005)
MCP/Wrist swollen joint count	0.42 (0.0061)	0.57 (0.0001)	0.08 (0.7076)	0.5 (0.0021)
MCP/Wrist tender joint count	0.37 (0.0161)	0.49 (0.0010)	0.12 (0.5464)	0.57 (0.0003)

[a] Correlation between baseline clinical activity score and baseline vascularity or thickness scores

[b] Correlation between week 24 changes in clinical activity score and week 24 changes in vascularity or thickness scores, filtered to include only subjects with baseline vascularity or thickness scores of at least 1, respectively

[c] Pearson's correlation coefficient r (p-value)

Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal joint

Figure legend

Figure 1: Sirukumab and Adalimumab Significantly Reduce Vascularity in Patients with Evidence of Baseline Vascularity. Change from baseline in (A) vascularity and (B) thickness scores (y-axis) at Week 2, 4, 8, and 24 visits after baseline (axis) are reported for subjects with an average baseline score ≥1 for the respective measure, stratified by treatment group (gray, adalimumab; white, sirukumab). Data displayed as box (median and interquartile range) and whiskers (5-95th percentiles) plots. ‡P <0.05 compared to Week 0 scores.

References

1. Taylor PC, Steuer A, Gruber J, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* 2004;50:1107-16. doi: 10.1002/art.20123
2. Seymour MW, Kelly S, Beals CR, et al. Ultrasound of metacarpophalangeal joints is a sensitive and reliable endpoint for drug therapies in rheumatoid arthritis: results of a randomized, two-center placebo-controlled study. *Arthritis Res Ther* 2012;14:R198. doi: 10.1186/ar4034
3. Seymour M, Petavy F, Chiesa F, et al. Ultrasonographic measures of synovitis in an early phase clinical trial: a double-blind, randomised, placebo and comparator controlled phase IIa trial of GW274150 (a selective inducible nitric oxide synthase inhibitor) in rheumatoid arthritis. *Clin Exp Rheumatol* 2012;30:254-61.
4. Taylor PC, Schiff MH, Wang Q, et al. Efficacy and safety of monotherapy with sirukumab compared with adalimumab monotherapy in biologic-naive patients with active rheumatoid arthritis (SIRROUND-H): a randomised, double-blind, parallel-group, multinational, 52-week, phase 3 study. *Ann Rheum Dis* 2018;77:658-66. doi: 10.1136/annrheumdis-2017-212496.
5. Ciurtin C, Brown G, Cotton A, Guinto J, Jones A, Morris V. THU0138 Das 28 correlated poorly with the objective evidence of inflammation as detected by ultrasound (US) examination of hands and feet in patients with established rheumatoid arthritis (RA) *Ann Rheum Dis.* 2017;76:253. dx.doi.org/10.1136/annrheumdis-2017-eular.3308
6. D'Agostino MA, Boers M, Wakefield RJ, et al. Do Ultrasound (Power Doppler Ultrasonography) and Disease Activity Score-28 Measure Different Aspects of Disease Activity? Analyses from an Open-Label Study of Power Doppler Ultrasonography Response Patients with Rheumatoid Arthritis Patients Starting Abatacept. *Rheumatology* 2015;54(Suppl 1) :i81-i82.

Competing interests: PCT has served as a consultant to AbbVie, Biogen, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer, Roche, and UCB Pharma and has received research grant funding from Celgene, Galapagos, Eli Lilly, and UCB Pharma. KS, BD, DdV, BH, IG, MJL At time of study were employed by Janssen Research & Development and owned stock in parent company Johnson & Johnson.

Contributorship: All authors meet the journal's criteria for authorship. All authors have contributed to the work and approve the presented findings.

Acknowledgements: PCT would like to acknowledge support by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and by AR UK.

Funding information: This study was funded by Janssen Research and Development.

Ethical approval information: The study protocols were reviewed and approved by an independent ethics committee or institutional review board for each study center. This study is registered at EudraCT (number: 2013-001417-32) and ClinicalTrials.gov (number: NCT02019472)

Data sharing: All data is included in this letter and attached tables and figures