Author’s response to reviews

Title: Ultrasound Detects Synovitis in Replaced and Other Surgically Operated Joints in Rheumatoid Arthritis Patients

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RE: Submission of Original Article

Dear Clinical and Experimental Rheumatology Editor,

Thank you for considering our manuscript for publication entitled, “Ultrasound Detects Synovitis in Replaced Joints in Rheumatoid Arthritis Patients” in BMC Rheumatology. We have carefully examined the comments posed by the reviewers and have prepared responses below. We still believe this is a novel ultrasound based rheumatoid arthritis (RA) study evaluating and quantifying synovitis in replaced joints, which despite their commonality have not been systematically characterized by objective imaging modalities such as ultrasound. It is frequently thought that when joints are replaced in RA, the synovium is removed and the joint should not develop synovitis. This study refutes that incorrect assumption. In addition, non-operated joints are well known to respond clinically and by ultrasound measures of synovitis to newer RA therapeutics, however surgically operated joints represent a relevant subpopulation otherwise ignored for the sake of clinical trials and longitudinal assessments. In this post-hoc analysis, we demonstrate that replaced joints exhibit increased baseline ultrasound synovitis compared to non-operated joints. Additionally, replaced joints demonstrate significant therapeutic response by both Power-Doppler and grayscale ultrasound measures, thereby identifying previously uncharacterized targets for therapy.

This manuscript represents original work and is not under consideration by any other journal. We
confirm that each individual named as an author meets the International Committee of Medical Journal Editors criteria for authorship and has given necessary attention to ensure the integrity of the work. Author contributions by project task are as follows: study design (EAC, VKR, DAE); data acquisition (EAC, GSK, JB, ARFS, VKR); data analysis and interpretation (EAC, GSK, JB, RDA, JF, ARFS, DAE, VKR); drafting manuscript (EAC, GSK, JB, RDA, JF, ARFS, DAE, VKR); and final draft approval (EAC, GSK, JB, RDA, JF, ARFS, DAE, VKR).

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Warm regards,

Veena Kittane Ranganath, MD, MS

We thank the editor and the reviewers for taking the time to aid in the improvement of our manuscript.

Reviewer 1:
Comment 1. The idea is very original, however, why did you combine prosthetic joint replacement surgeries with other osteoarticular operations (arthroscopy, joint fusion, tendon surgery and synovectomy) for ultrasonographic evaluation? Undoubtedly, these are two different scenarios to evaluate.

Author Response 1: We thank the reviewer for this comment. We apologize if we were not clear, however, we did separate out replaced joints and other operated joints (Methods page 6, Table 1). We agree it would have been ideal to examine each of the other operations (excluding replacements) categorized based on type of surgery, to evaluate baseline ultrasound features in these subsets individually, as well as improvement over time. However, this proved difficult for 2 reasons. 1) The small sample size hindered our ability to perform the analyses suggested by the reviewer, and is the primary challenge. 2) In addition, the surgical data was collected by patient report, physician directed detailed inquiry, and physical examination, with confirmation by surgical report in many cases. Thus, the completeness in the level of detail needed to subcategorize the surgeries may not have always been present. The following content was added (Methods, Page 6, paragraph 2): OJA included joint arthroscopies, joint fusion, synovectomies, and tendon surgeries; “these interventions were grouped together given their small sample sizes individually”.

Comment 2. In title: change prosthetic replacements for joint surgeries, since you evaluated both surgical situations.

Author Response 2: The title was adjusted in accordance to the reviewer’s comment. (Title, page 1, line 1): “Ultrasound Detects Synovitis in Replaced and Other Surgically Operated Joints in Rheumatoid Arthritis Patients.”

Comment 3. Ultrasonographic evaluation times were different between the two clinical trials initiated by the investigator. Also, two different drugs were used. It is not clear in the manuscript to which group each of the patients undergoing surgery belong. Could you add this information?
Author Response 3: We thank the reviewer for the recommendation. We performed a subgroup sensitivity analysis for each of the study drugs (tocilizumab [toci] vs tofacitinib [tofa]). We found that the results were largely consistent between the two drugs. PDUS and GSUS significantly improved between baseline and final assessment in naïve joints in both studies (p<0.01 for all comparisons). The magnitude of improvement was also very similar (ex. mean delta PDUS values of 0.23 and 0.3). In addition, we found similar findings across study drugs for replaced joints (PDUS improvement 0.65, p=0.05; and 0.8, p=0.06). For operated joints we found improvements in PDUS of 0.3 (p=0.28) vs 0.0 (p=0.99). Our conclusions from the individual studies are the same as the overall conclusions and we do not have reason to suspect that the results are influenced by drug type. Information was added to the statistical and results sections.

Comment 4. Despite the acceptable intra and inter-observer correlation of the two sonographers, they used two different machines to evaluate synovitis. Ideally, one should use the same device throughout the study. Could you justify this?

Author Response 4: Based on the reviewer’s comment, it appears that we were not clear. This methodology reflects two separate investigator-initiated clinical trials from which the data of our current manuscript was combined. As such, the methodology in this retrospective study reflects that of the parent clinical trials from which the data derives. The tocilizumab clinical study was performed at 2 locations with the same machine at both sites (MyLab70). The tofacitinib clinical study was performed at one clinical site with a different machine (GE LogicE9). Thus, the same ultrasound machine was used with each of the studies. The following content has been added (Methods, page 7, paragraph 2): MyLab70C US machine (Biosound Esaote, Fishers, IN) was used for image acquisition in the tocilizumab trial (12-18 MHz linear probe), whereas tofacitinib images were obtained using GE LogicE9 US machine (GE Healthcare, Chicago, IL) (6-15 MHz linear probe), as mandated in the respective parent clinical trials.

Comment 5. In methods: you should describe better how to assess US synovitis of the operated joints: location, cuts, artifacts, etc. Also try to describe the US grayscale and power Doppler scores (was it similar to joint assessment without surgery?)

Author Response 5: We thank the reviewer for the recommendation. The following content has been added (Methods, page 7, paragraph 3): …and medial/lateral parapatellar axial oblique views of the knees. B-mode scanning of replaced joints and OJA, including joint position and depth, were similar to that performed on native joints. In subjects with joint replacement, hardware artifacts could be recognized as well as material in the pseudocapsule. In most circumstances, Doppler signal was present within the visualized intracapsular material. Joints that could not be assessed by ultrasound (e.g. severe anatomical deformation) were excluded from the MSUS joint-level analyses. The following content has been added (Discussion, page 12, paragraph 2): At the trial onset, no replaced joint was devoid of baseline synovitis, unlike native joints which presented with synovitis less commonly and with lesser severity. The following content has been added (Discussion, page 13, paragraph 1): “…an outcome that further supports our study’s conclusions.(16) However, the difference in inflammation between joint types was still remarkable by end of study – with replaced joints demonstrating worse synovitis scores (PDUS: 1.56, and GSUS: 1.72) than native joints’ baseline (PDUS: 0.77, and GSUS: 1.18) – even when accounting for anatomical joint site. The clinical implications of MSUS synovitis is unclear…”

Reviewer 2:
No further comments
Author Response: Thank you for taking the time to review our manuscript.

Reviewer 3:
Comment 1. This study showed that measurable synovitis by MSUS exists in the area around replaced joints in patients with RA. I wonder whether there were any differences between replacement sites. (Small joint - MCP and PIP vs. large joint - knee)

Author Response 1: We thank the reviewer for their comment. We performed a similar sensitivity analysis for small vs large joints as we performed for the two different drugs. As with the two different drugs, small and large joints changed similarly to each other and to the overall set of findings within the set of naïve and operated joints. Both small and large joints PDUS scores improved significantly for naïve joints (P<0.001 for both) and did not change significantly for OJAs. We did find that small replaced joints improved (p=0.02) whereas large replaced joints did not significantly improve (p=0.5). This content was added to the statistical and results sections.