Reviewer's report

Title: Association between synovial fluid proinflammatory cytokines and radiographic grading and pain-related scores in 47 consecutive patients with osteoarthritis of the knee

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Reviewer: Virginia Kraus

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This study evaluates 44 synovial fluids from osteoarthritic knees. The two main study findings are quite interesting, that TNFalpha correlates strongly with symptoms (determined by WOMAC) and that IL-6 inversely correlates with structural severity.

The strengths of this paper are the fact that synovial fluid and not serum cytokines are being measured, as these are most proximal to the disease.

The weaknesses of this paper are: its lack of description of the kits/methods used for measurement of the cytokines, the CVs of the assays and level of detection (critical in case of NGF where nothing was measurable), the number of freeze thaws of the samples or how quickly the samples were stored and at what temperature after they were obtained. One presumes the synovial fluids were direct aspirates and not obtained by lavage (this should be clarified in the text).

The manuscript requires a native English speaker to edit it. The manuscript would also greatly benefit from major revision of the Discussion section. Currently it is rambling and the ideas should be consolidated and refined and focussed. The authors are encouraged to use the first two paragraphs to discuss the two main important findings, and an additional 1-3 paragraphs to discuss other issues such as limitations.

The work of Dr. Wim van den Berg should be cited – this was mouse work showing that TNFalpha inhibition in a mouse model of OA led to inhibition of synovitis, whereas, IL-1 inhibition led to inhibition of structural change. The authors work is compatible with these data.

The WOMAC version and the validity of the Japanese version should be discussed since correlation of TNFalpha with symptoms is a major finding in this paper.

The authors should consider semi-quantitative scoring the radiographs for osteophyte and joint space narrowing radiographic features using the OARSI atlas then evaluating for correlation with TNFalpha and IL-6. KL tends to obscure findings because it inappropriately combines the two separate pathophysiological processes of osteophyte and joint space narrowing. The results can sometimes be that a cytokine correlates with one feature and not another, or in one direction
with one feature and another direction with the other radiographic feature, leading to little or confusing results with KL.

Figure 1C should be deleted as NGF was undetectable. More discussion regarding this is required. Has anyone measured NGF is synovial fluid? If so, what is the difference between their method and the one used here?

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare I have no competing interests.