Author's response to reviews

Title: Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study

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Author's response to reviews: see over

Dear Judith Gorton

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The authors are delighted to hear that our manuscript "Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study" has been accepted for publication in BMC Musculoskeletal Disorders.

We appreciate your suggestions and have incorporated all of them with minor revisions (highlighted in yellow).

Associate editor's comments

The authors hypothesise that the groups may have been unbalanced but this was a randomised trial with reasonably sized groups and so, whilst this is possible, it is unlikely. I have taken the liberty of adjusting and shortening the added discussion, although the authors need not accept my changes.

Response

No dose effect was seen in this study and the canakinumab group receiving the additional loading dose did not demonstrate an increase in efficacy. It is possible that therapy led to differential up- or down-regulation of receptors or soluble receptors, including type 2 decoy receptors, involved in regulation of IL-1β activity, thereby resulting in paradoxical effects. Another factor could have been the relatively modest sample size. The results could be consistent with a subgroup of canakinumab-responsive patients, although randomization should have ensured equal distribution amongst dosing groups. It would be of great importance to identify biomarkers for patients with a good response to canakinumab, although our biomarker panel failed to identify any, potentially limited by technical factors. For example, diurnal variation in biomarker levels, such as IL-6, may have influenced the outcome.

The biological role of IL-1β in the disease pathogenesis of RA is not fully understood. Data from

anakinra studies suggest that there might be a relatively inferior biological role of IL-1β as compared to TNF-α in this disease. In a meta-analysis by the Cochrane group including 5 randomized trails involving 2876 patients (781 on placebo, 2065 on anakinra), anakinra 50-100 mg per day improved symptoms of pain, function, and stiffness over a 6-month period [5]. Significant improvements were noted for ACR 20 (38% vs 23% on placebo), which were considered clinically meaningful, although modest. ACR 50 was achieved by 18% vs 7%, and ACR 70 by 7% vs 2% of patients. The ACR 50 rates achieved in our study within 12 weeks in the canakinumab 150 mg q4wk group (26% vs 11% canakinumab vs placebo) compare favorably with the outcomes reported for anakinra.

In contrast, in sJIA IL-1β plays a major role in disease pathology in the majority of patients [7].

In addition, IL-1β plays also a key role in gouty arthritis inflammation, making targeted anti-IL-1β therapy an appropriate option [14,15]. In a phase II dose-ranging study in patients with acute gouty arthritis who were unable to receive NSAIDs and/or colchicine, canakinumab provided more rapid and sustained pain relief and significantly reduced the risk of new flares compared with triamcinolone acetonide 40 mg [8].

Looking forward to hearing back from you soon.

Regards
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