Response to: 'Correspondence on 'Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis' by Ruscitti *et al*

We were pleased to read the commentary on our recent article by Ruscitti *et al* and we share their interest in the potential role of inflammatory pathways in the development of metabolic disorders such as diabetes in patients with rheumatoid arthritis (RA).¹ Indeed, both interleukin (IL)-1 and IL-6 levels were independently associated with the development of diabetes in our original study, implicating them as potential mediators of metabolic changes that could lead to the development of diabetes.²

Observational research is, of course, limited to defining associations and cannot prove causality. In our study, as in many large observational studies, we were unable to assess total adiposity or to assess visceral fat content; factors that play an important role in diabetes risk and may not be adequately estimated by body mass index. Thus, there remains a risk of residual confounding and that some of the noted associations are correlative but not causative.

We therefore appreciate the discussion by Ruscitti *et al* regarding clinical trial and interventional data in this area. They provide discussion of important evidence to support improvements in glucose control in patients with both type-2 diabetes and RA that were treated with therapies directed against IL-1. While a recent large clinical trial found no benefit of canakinumab in terms of the reduction in the risk of diabetes in the general population,³ Ruscitti *et al* provide a discussion of important additional data that support the potential value of therapies that intervene on these pathways in patients with both RA and diabetes. Interestingly, the authors refer to some of their recent work supporting the possibility that anakinra, a therapy that blocks both IL-1 α and IL-1 β , might have a significant impact on reducing markers of insulin resistance in patients with RA and diabetes.⁴

The authors also discuss experimental models that demonstrate potential value of interfering with the IL-6 pathway on key pathways that are implicated in diabetes risk. While there remain limited clinical data studying the benefits of IL-6 therapies on insulin resistance and the risk of diabetes, a recent study demonstrated that sarilumab resulted in greater improvements in haemoglobin A1c levels compared with conventional therapies and antitumour necrosis factor therapies in patients with RA, with or without diabetes.⁵

We agree that these data are informative and support the hypothesis that these inflammatory pathways play a direct role in regulating the insulin resistance. Further study in this area is therefore of interest. However, it is worth acknowledging that large-scale interventional trials evaluating the role of specific therapies in reducing the incidence of diabetes among patients with RA may not be feasible.

Overall, we agree that there is mounting evidence that these inflammatory pathways play a role in the development of diabetes in the general population and in patients with RA. While there is still limited evidence to support the choice of a

particular therapy with the goal of reducing the risk of diabetes, it is perhaps realistic to believe that the future of rheumatology may include the consideration of diabetes and other comorbid outcomes to help guide the choice of therapy for an individual patient.

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Handling editor Josef S Smolen

Acknowledgements The contents of this work do not represent the views of the Department of the Veterans Affairs or the US Government.

Contributors All authors drafted the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Baker JF, England BR, Mikuls TR. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2021-220114

Received 9 February 2021

Accepted 11 February 2021

► <http://dx.doi.org/10.1136/annrheumdis-2021-220047>

Ann Rheum Dis 2021;0:1. doi:10.1136/annrheumdis-2021-220114

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REFERENCES

- 1 Ruscitti P, Sesti G, Cipriani P. Correspondence on "Disease activity, cytokines, chemokines, and the risk of incident diabetes in rheumatoid arthritis". *Annals of the Rheumatic Diseases* 2021. doi:10.1136/annrheumdis-2021-220047
- 2 Baker JF, England BR, George M, *et al*. Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis. *Ann Rheum Dis* 2021. doi:10.1136/annrheumdis-2020-219140
- 3 Everett BM, Donath MY, Pradhan AD, *et al*. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018;71:2392–401.
- 4 Ruscitti P, Masеду F, Alvaro S, *et al*. Anti-Interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (track): a multicentre, open-label, randomised controlled trial. *PLoS Med* 2019;16:e1002901.
- 5 Genovese MC, Burmester GR, Hagino O, *et al*. Interleukin-6 receptor blockade or TNF α inhibition for reducing glycaemia in patients with RA and diabetes: post hoc analyses of three randomised, controlled trials. *Arthritis Res Ther* 2020;22:206.