UNIVERSITY OF LEEDS

This is a repository copy of *Should we aim for personalized prevention in individuals at risk of rheumatoid arthritis?*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/168947/

Version: Accepted Version

**Article:**
Mankia, K and Emery, P orcid.org/0000-0002-7429-8482 (2021) Should we aim for personalized prevention in individuals at risk of rheumatoid arthritis? International Journal of Rheumatic Diseases, 24 (5). pp. 621-622. ISSN 1756-1841

https://doi.org/10.1111/1756-185X.14045

© 2021 Asia Pacific League of Associations for Rheumatology and John Wiley & Sons Australia, Ltd. This is the peer reviewed version of the following article: Mankia, K. and Emery, P. (2021), Should we aim for personalized prevention in individuals at risk of rheumatoid arthritis?. Int J Rheum Dis, 24: 621-622, which has been published in final form at https://doi.org/10.1111/1756-185X.14045. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. Uploaded in accordance with the publisher's self-archiving policy.

**Reuse**
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

**Editorial**

# Should we aim for personalised prevention in individuals at-risk of rheumatoid arthritis?

**Kulveer Mankia & Paul Emery**

k.s.mankia@leeds.ac.uk **(corresponding author)**

p.emery@leeds.ac.uk

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust.

Progress in our understanding of preclinical rheumatoid arthritis (RA) has been driven largely by clinical and laboratory data from prospective cohorts of at-risk individuals. These include large, well-characterised populations of relatives of RA patients and also auto-antibody positive individuals with musculoskeletal symptoms (1, 2). More than a decade of observational data from these cohorts has identified risk factors and biomarkers which are associated with progression to clinical arthritis and RA. Consequently, risk stratification is now feasible, enabling case selection for preventative intervention.

How to approach RA prevention is a major contemporary challenge in rheumatology, with important implications for the other autoimmune diseases. A logical strategy in RA is to extend the 'early arthritis model', where prompt immunotherapy can induce drug free remission in patients with early clinical synovitis (3). As such, use of immunotherapies in high risk individuals without clinical synovitis, are being tested. However, some individuals, especially those with a lower absolute risk of arthritis development may be reluctant to take immunosuppressive drugs, for fear of over-treatment or side-effects. An alternative and perhaps complementary paradigm would be to target specific risk factors with more conservative interventions, thus personalising prevention according to the biological drivers of disease in any given at-risk individual.

One advantage of this more nuanced approach is that different reversible risk factors for anti-citrullinated protein antibodies (ACPA) and disease progression can already be identified and targeted. Such risk factors may be influenced by lifestyle modification, and non-pharmacological health intervention. For example, cigarette smoking is strongly associated with ACPA and the development of RA; it drives periodontal disease and may also influence the initiation of RA-autoimmunity at the lung. Periodontal disease is itself more prevalent in at-risk individuals (both

ACPA positive individuals without clinical synovitis and first-degree relatives of RA patients), independently of smoking status (4, 5). Periodontal bacteria such as *Porphyromonas gingivalis* are capable of citrullination and triggering ACPA production (6, 7). Furthermore, periodontal inflammation and lung inflammation are detectable in at-risk individuals who have not yet developed joint inflammation (4, 8). As such, focusing on smoking cessation and/or periodontal intervention in at-risk individuals who have these risk factors may have multiple benefits; both may directly prevent disease progression as well as being associated with broader health benefits to the individual, without the associated risks of pharmacotherapy. Similarly, elevated body mass index (BMI) and dyslipidaemia have been identified as independent risk factors for arthritis development in cohorts of at-risk individuals. Addressing these risk factors should also provide broader systemic health benefits. Achieving behavioural change in the busy clinic environment, however, is associated with its own set of challenges. Bespoke clinical pathways for at-risk individuals are likely to be required.

Clinical trials will be required to test whether such personalised approaches to prevention will be acceptable to at risk individuals and if so, whether they effectively modulate disease progression, either alone, or in combination with immunotherapy. The most relevant outcomes for such trials are also a matter for debate; trial end-points should not just be restricted to the development of clinical arthritis but could also include other important end-points such as absolute risk reduction (how different is that to reduced development of arthritis) or improvement in symptoms or quality of life.

A future strategy may be to comprehensively assess a panel of risk factors (including reversible ones) in all at-risk individuals, as well as the overall absolute risk of arthritis in the short and medium term. In those with low absolute risk of arthritis, targeted risk factor modification in the short and medium term alone, with close observation, may be the preferred strategy. Absolute risk reduction, the progression of disease (e.g. development joint involvement on imaging) and/or improvement of symptoms and quality of life may be the right outcomes. Conversely, in those at high risk (often subclinical joint involvement already present) (is this aimed at image screening of joints in such high risk persons), risk factor modification with additional immunotherapy may be more appropriate, with the objective of short-term arthritis prevention. Advances in the treatment of RA have taught us that ‘one size does not fit all’ and personalised treatment is now the agreed goal. This lesson should be applied to RA prevention.

1. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Annals of the rheumatic diseases. 2015;74(9):1659-66.
2. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Annals of the rheumatic diseases. 2013;72(12):1920-6.
3. Burgers LE, Allaart CF, Huizinga TWJ, van der Helm-van Mil AHM. Brief Report: Clinical Trials Aiming to Prevent Rheumatoid Arthritis Cannot Detect Prevention Without Adequate Risk Stratification: A Trial of Methotrexate Versus Placebo in Undifferentiated Arthritis as an Example. Arthritis & rheumatology (Hoboken, NJ). 2017;69(5):926-31.
4. Mankia K, Cheng Z, Do T, Hunt L, Meade J, Kang J, et al. Prevalence of Periodontal Disease and Periodontopathic Bacteria in Anti-Cyclic Citrullinated Protein Antibody-Positive At-Risk Adults Without Arthritis. JAMA Netw Open. 2019;2(6):e195394.
5. Bello-Gualtero JM, Lafaurie GI, Hoyos LX, Castillo DM, De-Avila J, Munevar JC, et al. Periodontal Disease in Individuals With a Genetic Risk of Developing Arthritis and Early Rheumatoid Arthritis: A Cross-Sectional Study. Journal of periodontology. 2016;87(4):346-56.
6. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, et al. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis and rheumatism. 2010;62(9):2662-72.
7. Harvey GP, Fitzsimmons TR, Dhamarpatni AA, Marchant C, Haynes DR, Bartold PM. Expression of peptidylarginine deiminase-2 and -4, citrullinated proteins and anti-citrullinated protein antibodies in human gingiva. Journal of periodontal research. 2013;48(2):252-61.
8. Demoruelle MK, Weisman MH, Simonian PL, Lynch DA, Sachs PB, Pedraza IF, et al. Brief report: airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: early injury or initiating site of autoimmunity? Arthritis and rheumatism. 2012;64(6):1756-61.