EDITORIAL

Rheumatoid arthritis prevention: any takers?

Marie Falahee,1 Karim Raza

Our understanding of biological mechanisms operating at articular and extra-articular sites in individuals ‘at risk’ of rheumatoid arthritis (RA) has increased significantly over recent years.1 In parallel, there has been significant progress in the prediction of RA development in those at risk.2 This has opened up an agenda for research on possibilities for intervention in pre-RA phases, and opportunities for both primary and secondary prevention have been identified.3–5

Intervention at the very earliest stages of disease development could, in theory, control symptoms such as arthralgia and fatigue that often precede the development of clinical arthritis,6 delay the onset of RA, reduce the likelihood of RA developing and/or reduce the severity of RA if it were to develop. While the evidence base to support such strategies is in its infancy, B-cell depletion, with a single infusion of 1000 mg of rituximab, has been shown to significantly delay the onset of RA in individuals with autoantibody-positive arthralgia and either an inflammatory response as measured by C-reactive protein or subclinical synovitis on imaging.7 Similarly, the impact of time-limited courses of other immunomodulatory therapies, including abatacept8 and hydroxychloroquine,9 on arthritis and RA development is being assessed in other at-risk groups. Results of these studies,8,9 where the intervention is given for 12 months, and other studies, where interventions are given for different but nevertheless time-limited durations, are awaited with interest. Preventive strategies are also under investigation in other chronic autoimmune conditions. For example, an anti-CD3 antibody has recently been shown to significantly delay progression to type 1 diabetes in non-diabetic relatives of patients identified as being at high risk on the basis of the presence of diabetes-related auto-antibodies and other risk factors.10

To have clinical impact, therapeutic approaches identified as being effective in reducing the risk of RA need to be acceptable to those at risk. Previous qualitative research has identified that individuals at risk of RA have concerns about taking ‘preventive’ medicines.11 In this issue of RMD Open, van Boheemen et al12 report on the perspectives of individuals who had declined participation in, and also who had participated in, one of the two RA prevention trials: the STAtins to Prevent Rheumatoid Arthritis trial (RMD open to insert Ref) and the Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept trial.8 Challenges to participant recruitment in trials of patients with seropositive arthralgia raise some important issues for the rheumatology research community to consider and reflect the importance of understanding the preferences of at-risk individuals about benefits and risks of interventions in relation to the disease they are at risk of.12

Public perceptions about RA are often inaccurate: many do not perceive RA to be a serious disease, and some view it as an inevitable consequence of ageing.13,14 Individuals with these views may be less likely to accept preventive therapeutic interventions—this was certainly a theme identified by van Boheemen et al. Positive views about RA prediction and prevention are often associated with misperceptions around what being at ‘high risk’ means (eg, some interpret this to mean that they will definitely develop RA) and the likely benefit of ‘preventive’ therapy (eg, for some this means the therapy will definitely prevent them from developing RA).15–17 The development of effective communication tools around predictive testing, preventive interventions and RA itself is therefore essential to facilitate informed decision-making. Although predictive algorithms exist, they do not fully address issues around the time course of RA development or the likely severity of RA after it has developed, which are key considerations for decision-making about preventive therapy. Further research to facilitate comprehensive risk assessment for RA is an essential precursor to the development of effective communication tools around predictive testing, preventive interventions, and RA itself.
of effective informational resources for individuals for whom preventive treatment may be appropriate.

Non-pharmacological interventions are preferred by some at-risk individuals, especially for those without symptoms (eg, autoantibody-positive individuals and those with genetic risk factors)\(^1 15–19\) van Boheemen\(^ et\)\(^ al\)\(^\). Initial evidence suggests that personalised risk information about RA has a positive impact on behavioural intentions and risk-reducing behaviour\(^20\) while providing reassurance to recipients.\(^21\) Although several ongoing studies are investigating pharmacological interventions to prevent arthritis development, no interventional trials of promising behavioural interventions, particularly smoking cessation,\(^22\)\(^23\) to reduce risk of RA development and progression have been published. Investigation in this area is needed.

Preventive therapies for other conditions are well established in routine clinical practice; statins and antihypertensive medications are widely prescribed to reduce the risk of ischaemic heart disease and bisphosphonates to reduce the risk of fracture. Many entirely asymptomatic individuals with conditions such as hypercholesterolaemia, hypertension and osteoporosis accept such pharmacological therapies. Indeed, for these conditions, long-term, often lifelong, preventive treatment is both required and often accepted. As yet, no pharmacological treatments have been shown to reduce the risk of RA development in the medium to long term. However, this remains an active and important area of research. We need to learn from experiences in other chronic diseases and address the barriers identified by van Boheemen\(^ et\)\(^ al\)\(^\) that hinder the efficient development of preventive strategies for the management of RA. Endavouring to overcome such barriers is likely to be worthwhile, given that a ‘preventive’ approach in RA has clear potential to reduce pain and disability as well as societal costs resulting from lost productivity and healthcare usage at huge scale.

REFERENCES

1. Tracy A, Buckley CD, Raza K. Pre-Symptomatic autoimmunity in rheumatoid arthritis: when does the disease start? Semin Immunopathol 2017;39:423–35.
2. van Boheemen L, van Schaardenburg D. Predicting rheumatoid arthritis in at-risk individuals. Clin Ther 2019;41:1296–98.
3. Raza K, Klareskog L, Holers VM. Predicting and preventing the development of rheumatoid arthritis. Rheumatology 2016;55:1–3.
4. van Steenbergen HW, da Silva JAP, Huizinga TWJ, et al. Preventing progression from arthralgia to arthritis: targeting the right patients. Nat Rev Rheumatol 2017;13:480–41.
5. Stanway JA, Isaacs JD. Tolerance-inducing medicines in autoimmunity: rheumatology and beyond. Lancet Rheumatol 2020;2:e665–75.
6. van Beers-Tas MH, Ter Wee MM, van TuyL LH, et al. Initial validation and results of the symptoms in persons at risk of rheumatoid arthritis (SPARRA) questionnaire: a EULAR project. RMD Open 2018;4:e000641.
7. Gerlag DM, Safy M, Maijer KL, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. Arthritis Rheumatol 2019;78:179–85.
8. Al-Laith M, Jasenecova M, Abraham S, et al. Arthritis prevention in the pre-clinical phase of RA with abatacept (the APIPPRA study): a multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial protocol. Trials 2019;20:429.
9. Strategy to prevent the onset of Clinically-Apparent rheumatoid arthritis (StopRA). Available: http://clinicaltrials.gov/ct2/show/NCT02603146.
10. Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, Tepilizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019:381–93.
11. Mosor E, Stoffer-Marx M, Steiner G, et al. I would never take preventive medication! perspectives and information needs of people who underwent predictive tests for rheumatoid arthritis. Arthritis Care Res 2020;72:630–41.
12. Falahae M, Finckh A, Raza K, et al. Preferences of patients and at-risk individuals for preventive approaches to rheumatoid arthritis. Clin Ther 2019;41:1346–54.
13. Simons G, Belcher J, Morton C, et al. Symptom recognition and perceived urgency of help-seeking for rheumatoid arthritis and other diseases in the general public: a mixed method approach. Arthritis Care Res 2017;69:633–41.
14. Simons G, Mason A, Falahae M, et al. Qualitative exploration of illness perceptions of rheumatoid arthritis in the general public. Musculoskeletal Care 2017;15:13–22.
15. Falahae M, Simons G, Buckley CD, et al. Patients’ perceptions of their relatives’ risk of developing rheumatoid arthritis and of the potential for risk communication, prediction, and modulation. Arthritis Care Res 2017;69:1558–65.
16. Simons G, Stack RJ, Stoffer-Marx M, et al. Perceptions of first-degree relatives of patients with rheumatoid arthritis about lifestyle modifications and pharmacological interventions to reduce the risk of rheumatoid arthritis development: a qualitative interview study. BMC Rheumatol 2018;2:31.
17. Stack RJ, Stoffer M, Engbrecht M, et al. Perceptions of risk and predictive testing held by the first-degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: a qualitative study. BMJ Open 2016;6:e010555.
18. Munro S, Spooner L, Milbers K, et al. Perspectives of patients, first-degree relatives and rheumatologists on preventive treatments for rheumatoid arthritis: a qualitative analysis. BMC Rheumatol 2018;2:18.
19. van Boheemen L, Bolt JW, Ter Wee MM, et al. Patients’ and rheumatologists’ perceptions on preventive intervention in rheumatoid arthritis and axial spondyloarthritis. Arthritis Res Ther 2020;22:217.
20. Sparks JA, Iversen MD, Yu Z, et al. Disclosure of personalized rheumatoid arthritis risk using genetics, biomarkers, and lifestyle factors to motivate health behavior improvements: a randomized controlled trial. Arthritis Care Res 2018;70:823–33.
21. Marshall AA, Zaccarelli A, Yu Z, et al. Effect of communicating personalized rheumatoid arthritis risk on concerning for developing RA: a randomized controlled trial. Patient Educ Couns 2019;102:976–83.
22. Källberg H, Ding B, Padyukov L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70:508–11.
23. Liu X, Tedeschi SK, Barbhaiya M, et al. Impact and timing of smoking cessation on reducing risk of rheumatoid arthritis among women in the nurses’ health studies. Arthritis Care Res 2019;71:914–24.