doi.org/10.58931/crt.2025.2265

About the Authors

Liam O'Neil, MD, MHSc, FRCPC

Dr. Liam O'Neil is an Assistant Professor of Medicine and Immunology at the University of Manitoba in Winnipeg, Canada. His research program aims to understand the pre-clinical Rheumatoid Arthritis period by interfacing proteomics and systems immunology. He is the NPI of a longitudinal research cohort of ACPA positive individuals without RA, who are monitored for disease onset.

Affiliations: University of Manitoba, Department of Internal Medicine, Winnipeg, Canada

Hani El-Gabalawy, MD, FRCPC

Dr. Hani El-Gabalawy, MD, FRCPC is a Professor of Medicine and Immunology at the University of Manitoba, where he also holds the Endowed Rheumatology Research Chair and serves as a senior clinician-scientist. His research focuses on the immunopathogenesis and prevention of rheumatoid arthritis, specifically through collaborative research with First Nations communities.

Affiliations: University of Manitoba, Department of Internal Medicine, Winnipeg, Canada.

What Can We Tell Our Patients About Rheumatoid Arthritis Risk?

Liam O'Neil, MD, MHSc, FRCPC
Hani El-Gabalawy, MD, FRCPC

Introduction

You are seeing a 45-year-old female with a chief complaint of joint pain in the hands and feet. The symptoms have been apparent for 6 months. There was no preceding illness. She reports morning stiffness of the affected joints. The patient denies any joint swelling. Her medical history is notable for a strong family history of Rheumatoid Arthritis, and she currently smokes one pack of cigarettes daily. On physical examination, the joints appear normal, with full range of motion and no obvious tenderness to palpation. There is no evidence of synovitis or rashes. Laboratory investigations show elevated anti-citrullinated protein antibody level of 135, and her rheumatoid factor level is 45. C-reactive protein is within normal limits. Radiographs of the hands and feet are normal.

Questions:
1. What is her likelihood of developing rheumatoid arthritis within the next 3 years?
2. Are there any other tests you need to order?
3. Can rheumatoid arthritis be prevented in this individual? What advice can you provide her?

Rheumatoid Arthritis (RA) is an autoimmune inflammatory arthritis of unknown etiology. RA patients typically present with joint swelling in the hands and feet along with serological markers such as anti-citrullinated protein antibodies

(ACPA) and Rheumatoid Factor (RF).[1] RA is thought to begin with a set of risk factors, including genetics, sex, and environmental influences. Although numerous genetic loci have been linked to RA development, RA is strongly associated with the presence of a specific HLA-DRB1 risk allele termed the shared epitope.[2] Females are more predisposed to develop RA compared to males (often with a ratio of 4:1), and while this association is poorly understood, sex hormones and pregnancy likely play an important role. The external environment is also associated with RA development. Dietary factors, for example diets that are low in omega-3 fatty acids; (these are derived primarily from fish), along with environmental exposures such as air pollution and cigarette smoke are all linked to RA.[3] Having a first-degree relative with RA increases an individual's risk of developing the disease, likely due to a contribution of shared genetic factors and potentially similar environmental exposures. Approximately 70% of RA cases are seropositive (ACPA/RF positive), and in those that do develop autoantibodies, these appear years before the onset of clinically detectable arthritis. As such, ACPA has served as one of the best prediction markers for RA development. Although RA may start abruptly, many individuals experience non-specific joint symptoms suggestive of RA such as pain and stiffness in the hands and feet prior to the development of evident inflammatory arthritis.

What Is Her Likelihood Of Developing RA Within The Next 3 Years?

Research cohorts comprised of individuals at risk for developing RA have provided key insights into the pathogenesis of the preclinical disease stages of RA. Depending on the inclusion criteria for enrolment, a varying proportion of participants in these studies will develop RA after extended follow-up. Comparing those who develop RA with those who do not provides the opportunity to identify factors that are predictive of these outcomes. The individual in question has several important risk factors to suggest the risk of developing RA is quite high. Her family history of RA perhaps suggests that her polygenic risk score may be high, and although genotyping data are typically not clinically available, perhaps she carries the shared epitope HLA-DRB1 risk allele. Assuming she does, this allele has been shown in prior studies (mostly case-control) to interact synergistically with cigarette smoking (another risk factor in her case) by increasing the risk of RA by up to 15-fold.[5] She also meets all the criteria for clinically suspect arthralgia (CSA), in which approximately 20% of individuals develop arthritis within 2 years, though estimates vary.[6] The detection of ACPA has been demonstrated to be a highly reliable biomarker for predicting future RA. Moreover, the concentration of ACPA is an independent predictor for developing RA, with higher antibody levels corresponding to a greater risk of disease development.[7] Additionally, the presence of both ACPA and RF further increases the risk of developing RA.[8] While the exact risk associated with ACPA positivity varies depending on the cohort and testing methods used, approximately 35% of ACPA-positive individuals develop RA within 5 years.[7] Importantly, in individuals with both ACPA positivity and small joint arthralgia, the risk of progressing to clinical RA may be as high as 40% within 2 years. You counsel her that her risk of developing RA within the next 3 years likely exceeds 40%.

Are There Any Other Tests You Need To Order?

Several studies have examined the role of imaging modalities in predicting the risk of RA, specifically the use of ultrasound (US) and magnetic resonance imaging (MRI), with a focus on detecting subclinical synovitis. In US, the most specific findings suggestive of future RA include power Doppler signal, grey scale abnormalities and erosions. For MRI, features such as bone marrow edema, tenosynovitis/synovitis, and erosions are considered highly specific. In general, imaging findings in preclinical RA lack sensitivity, and as such, their absence does not rule out future RA in individuals with other risk factors. Among those with arthralgia, the combination of ACPA positivity and MRI-detected inflammation is associated with progression rates as high as 70%.[6] However, in the same study, the rate of progression among ACPA-negative individuals with MRI-detected inflammation was much lower, at 18%. Similarly, US findings in ACPA-positive individuals with arthralgia, the presence of bone erosion and synovitis was associated with a progression rate of 68% within 2 years. In contrast, when US findings were absent, the rate dropped to 15%.[9] To support risk stratification, comprehensive scoring systems have been developed in arthralgia cohorts, through weighted variables to generate a risk score allow for risk stratification of RA. Clinical features such as arthralgia, morning stiffness,

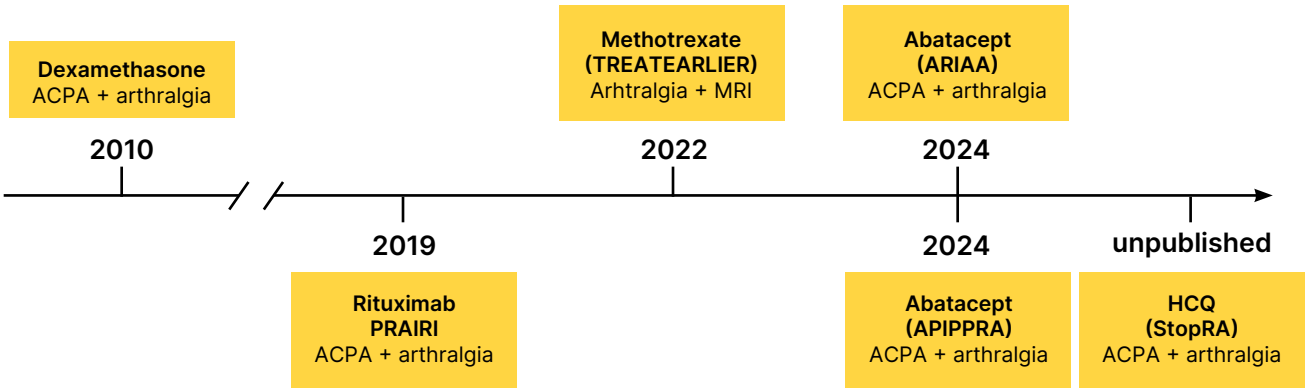

Figure 1. A summary of completed Rheumatoid Arthritis Prevention clinical trials and their major inclusion criteria; *courtesy of Liam O'Neil, MD, MHSc, FRCPC and Hani El-Gabalawy, MD, MHSc, FRCPC*

Abbreviations: ACPA: anti-citrullinated protein antibodies; **MRI:** magnetic resonance imaging

ACPA, and RF can collectively achieve thresholds of risk that exceed 50%.[10] While imaging likely provides added value, the cost-benefit of these approaches, particularly in very high-risk clinical profiles, remains somewhat unclear.

Magnetic resonance imaging or ultrasound can help detect subclinical synovitis and may aid in predicting future RA.

However, routine use of these imaging tests may not be feasible in many centres, and their added value in individuals with very high-risk profiles needs to be clarified. It is also uncertain what to do with positive results on imaging without clinical synovitis.

Can RA Be Prevented In This Individual? What Advice Can You Provide Her?

The first clinical trial aimed at RA prevention was published in 2010 and evaluated the effects of dexamethasone or placebo in 83 individuals with arthralgia and RA-related autoantibodies.[11] This trial showed no difference in the development of clinical arthritis after 2 years. This initial trial was followed by several others investigating repurposed RA medications including rituximab,[12] methotrexate,[13] abatacept[8,14] and hydroxychloroquine **(Figure 1)**. Largely, these trials shared a similar design, which was to provide participants with the active drug for a defined period (6 to 12 months), followed by a withdrawal period where individuals received no therapy. Rituximab, methotrexate, and abatacept showed efficacy in delaying the onset of RA during the active treatment phase. However, this protective effect tended to decrease during the treatment-free period. In 2 RCTs using abatacept, the preventative effects of the intervention remained statistically significant through the study follow-up period, showing sustained prevention of inflammatory arthritis.[13,14] However, long term follow up data shows that prevention disappears after about 3 years.[15] This finding differs from methotrexate and rituximab trials, which did not show persistent prevention of ACPA+ RA at the end of follow-up. In a subgroup analysis, methotrexate was shown to prevent ACPA- RA in individuals with joint pain and MRI inflammation.[16] Hydroxychloroquine and atorvastatin have not been shown to prevent RA among ACPA-positive individuals with arthralgia. Notably, the VITAL study, which was a placebo-controlled study evaluating 5 years of vitamin D and Omega-3 fatty acid supplementation, showed a preventative effect on the incidence of autoimmune disease, including a reduction in RA risk.[17] The total number of RA cases were low, and this was a pre-specified exploratory endpoint, rather than a primary outcome of the study. Further, since the study population was not screened for ACPA at baseline, it remains unclear how applicable these findings are to individuals with high-risk profiles.

Currently, there are no specific guidelines for managing individuals at risk of developing RA. Therefore, any advice provided should be pragmatic, focusing on lifestyle modifications that may reduce risk, while clearly acknowledging the limited evidence supporting these strategies.[18] A notable example is advocating for smoking cessation. Smoking is a well-established risk factor for RA and is associated with poor disease outcomes once RA develops. Moreover, all

individuals who smoke should be encouraged to quit due to the broader health risks associated with smoking, including cancer, cardiovascular disease, and chronic obstructive pulmonary disease. Diet is another modifiable factor; some evidence suggests that diets rich in omega-3 fatty acids, such as the Mediterranean diet or omega-3 fatty acid supplementation, may help reduce RA risk,[3] a finding supported by the VITAL study. Similar to smoking cessation, dietary changes may also offer broader health benefits. Finally, given the relatively high likelihood of progression to RA, annual follow-up is a reasonable approach. Educating individuals about the early signs and symptoms of RA will aid in timely diagnosis and treatment, which is known to significantly improve long-term outcomes.

Currently, there are no treatment guidelines for preventing RA, and further studies are needed before interventions can be recommended. Practical advice that can be provided to this patient includes: 1) Annual follow-up and education 2) Strongly advise her to quit smoking and provide her with resources to help her quit, and 3) Dietary changes.

Correspondence

Liam O'Neil, MD, MHSc, FRCPC
Email: liam.oneil@umanitoba.ca

Financial Disclosures

L.O.: Consulting: Organon, Fresenius Kabi, Abbvie and UCB.

References

1. Gravallese EM, Firestein GS. Rheumatoid Arthritis - Common Origins, Divergent Mechanisms. N Engl J Med 2023;388:529-42.
2. Laki J, Lundstrom E, Snir O, et al. Very high levels of anti-citrullinated protein antibodies are associated with HLA-DRB1*15 non-shared epitope allele in patients with rheumatoid arthritis. Arthritis Rheum 2012;64:2078-84.
3. Maisha JA, El-Gabalawy HS, O'Neil LJ. Modifiable risk factors linked to the development of rheumatoid arthritis: evidence, immunological mechanisms and prevention. Front Immunol 2023;14:1221125.
4. Padyukov L, Silva C, Stolt P, et al. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004;50:3085-92.
5. van Steenbergen HW, Mangnus L, Reijnierse M, et al. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis 2016;75:1824-30.
6. Bemis EA, Demoruelle MK, Seifert JA, et al. Factors associated with progression to inflammatory arthritis in first-degree relatives of individuals with RA following autoantibody positive screening in a non-clinical setting. Ann Rheum Dis 2021;80:154-61.
7. Tanner S, Dufault B, Smolik I, et al. A Prospective Study of the Development of Inflammatory Arthritis in the Family Members of Indigenous North American People With Rheumatoid Arthritis. Arthritis Rheumatol 2019;71:1494-503.
8. Cope AP, Jasenecova M, Vasconcelos JC, et al. Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial. Lancet 2024;403:838-49.
9. Di Matteo A, Mankia K, Duquenne L, et al. Ultrasound erosions in the feet best predict progression to inflammatory arthritis in anti-CCP positive at-risk individuals without clinical synovitis. Ann Rheum Dis 2020;79:901-7.
10. Duquenne L, Hensor EM, Wilson M, et al. Predicting Inflammatory Arthritis in At-Risk Persons: Development of Scores for Risk Stratification. Ann Intern Med 2023;176:1027-36.
11. Bos WH, Dijkmans BA, Boers M, et al. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: a randomised trial. Ann Rheum Dis 2010;69:571-4.
12. Gerlag DM, Safy M, Maijer KI, et al. Effects of B-cell directed therapy on the preclinical stage of rheumatoid arthritis: the PRAIRI study. Ann Rheum Dis 2019;78:179-85.
13. Krijbolder DI, Verstappen M, van Dijk BT, et al. Intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden (TREAT EARLIER): a randomised, double-blind, placebo-controlled, proof-of-concept trial. Lancet 2022;400:283-94.
14. Rech J, Tascilar K, Hagen M, et al. Abatacept inhibits inflammation and onset of rheumatoid arthritis in individuals at high risk (ARIAA): a randomised, international, multicentre, double-blind, placebo-controlled trial. Lancet 2024;403:850-9.
15. A. C, M. J, J. V, et al. OP0004 ABATACEPT IN INDIVIDUALS AT RISK OF DEVELOPING RHEUMATOID ARTHRITIS: RESULTS FROM THE ARTHRITIS PREVENTION IN THE PRE-CLINICAL PHASE OF RA WITH ABATACEPT LONG TERM OUTCOMES (ALTO) STUDY. EULAR; 2025; Barcelona, Spain: Annals of the Rheumatic Diseases. p. 4-5.
16. Dumoulin QA, Krijbolder DI, Visser K, et al. Development of rheumatoid arthritis after methotrexate in anticitrullinated protein antibody-negative people with clinically suspect arthralgia at risk of rheumatoid arthritis: 4-year data from the TREAT EARLIER trial. Lancet Rheumatol 2024;6:e827-e36.
17. Costenbader KH, Cook NR, Lee IM, et al. Vitamin D and Marine n-3 Fatty Acids for Autoimmune Disease Prevention: Outcomes Two Years After Completion of a Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol 2024;76:973-83.
18. O'Neil LJ, Alpizar-Rodriguez D, Deane KD. Rheumatoid Arthritis: The Continuum of Disease and Strategies for Prediction, Early Intervention, and Prevention. J Rheumatol 2024;51:337-49.