Innovation to Improve Outcomes in Indigenous People at Risk of RA

By Hani El-Gabalawy, MD, FRCPC, FCAHS

Multiple studies from our Manitoba-based clinical research group, along with studies from several other groups in Canada, U.S., and Mexico, have demonstrated that many Indigenous North American (INA) populations have increased risk of developing seropositive rheumatoid arthritis (RA). In these populations, the prevalence of RA can be 2-3 times higher than that observed in most other populations, the disease is more severe and disabling, and the outcomes are often unfavourable, with an excess burden of morbidity and mortality. The basis for this involves a complex interaction between biological, environmental, sociocultural, and health care delivery variables which are notoriously difficult to untangle. This is a challenge that is in much need of innovation.

As such, an innovation agenda that aims to improve the outcomes of RA in INA people needs to take into account the unique challenges inherent in the design of clinical studies, as well as in the implementation and the scalability of the proposed interventions resulting from these studies. During my tenure as a Canadian Institute of Health Research (CIHR) Scientific Director, I became involved with a visionary and unique strategic initiative led by the Institute of Aboriginal People's Health entitled Pathways to Health Equity for Aboriginal Peoples (*cihr-irsc.gc.ca/e/47003.html*). At the time I became involved, the scope of this strategic (so called signature) initiative had already been determined to focus on the compelling challenges of mental wellness, diabetes/obesity, tuberculosis, and oral health. In hindsight, had I been able to engage with this initiative on the ground floor at its inception, perhaps RA would have been one of the chosen focus areas, but "this is history" to quote an old phrase.

Nevertheless, there was much to learn from the Pathways initiative about how to approach an innovation agenda for INA People. The initiative, which was firmly grounded in the principles of Community Based Participatory Research (*ethics.gc.ca/eng/tcps2-eptc2_2018_chapter9-chapitre9.html*), had several incremental phases where nascent ideas were first explored in various communities based on modest levels of funding, and successful research groups and ideas were then supported with larger funding envelopes to begin to address the implementation and the scalability of the projects. It seems to me that this is the appropriate "pathway" to accomplishing what we need to achieve for devastating diseases such as RA in INA.

The work of my own research group has focused on the prediction and prevention of RA in First Nations. We have been fortunate to receive uninterrupted CIHR funding for this program since 2005 through open competitions and strategic initiatives such as the Human Immunology Research Teams program. We have made important observations regarding the risk of developing RA in INA by longitudinally studying the at-risk first-degree relatives (FDR) of INA RA patients. For example, we have shown that development of anti-citrullinated protein antibodies (ACPA) is common in the FDR, but that this is far from being a one-way street leading to RA development (PMID 30861615). Indeed, a substantial proportion of ACPA+ FDR reverted back to a seronegative state, and those destined to develop RA exhibited unique glycosylation patterns of their ACPA (PMID 31067000) and specific proteomic features (PMID 32770634).

We are currently engaged in an exciting initiative where we aim to reduce the risk of future RA development using a combination of anti-inflammatory/immunomodulatory nutritional supplements. This is based on findings from a collagen-induced arthritis mouse model of RA development, where our group showed that a combination of vitamin D, omega-3, and curcumin supplements was highly effective in attenuating the onset of arthritis in this model, with the curcumin contributing the most to this effect (PMID 33494792). We have begun the long road to the clinical translation, evaluation, and implementation of this approach in INA individuals at risk for developing RA. We remain inspired by the sensible approach that was developed in the CIHR "Pathways" signature initiative.

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