Rheumatoid arthritis—can its onset be delayed or prevented?

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that leads to significant health issues as well as high treatment costs. In this themed issue of *Clinical Therapeutics*, experts review multiple aspects of RA detection and intervention with the overall goal of moving the field closer to developing effective preventive measures. Identifying people before they develop the disorder could significantly alter the course of disease and spare people its damaging effects.

RA affects around one percent of the population worldwide. It leads to swollen, painful joints and can also damage other body systems such as the skin, eyes, lungs, heart, and blood vessels. This debilitating disease results in diminished quality of life, loss of work, pain, and suffering. It is also largely a "forever" disease from which patients with full-blown RA will suffer for the rest of their lives. While medications can control RA for many patients, very few experience a complete cure and are able to discontinue treatment. RA is an expensive disease. In the United States it currently costs around $20,000-30,000 per patient annually for treatment.

Guest-edited by Kevin D. Deane, MD, Ph.D., Associate Professor of Medicine, Division of Rheumatology, Department of Medicine University of Colorado Denver School of Medicine, Denver, CO, USA; and Tsang Tommy Cheung, MBBS (HK), Clinical Assistant Professor, Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, this themed issue taps into the expertise of many scientists across the world and discusses multiple aspects of RA

prevention. "These discussions will hopefully provide insights into how we can move RA forward to the point where we are preventing disease and also give guidance on how other autoimmune diseases could be prevented as well," explain the Guest Editors.

Many studies are already underway to learn how to prevent RA, however, prevention of autoimmune diseases is still new territory and there is a lot to discuss and learn. "Most people are familiar with prevention for diseases such as diabetes, heart disease, or cancer," notes Dr. Deane. "For example, it is very common for someone to have routine blood tests, which might reveal high cholesterol, a potential risk factor for a future heart attack. That individual can then implement lifestyle changes like more healthful eating, smoking cessation, and more exercise, or taking a medication to lower the risk of a future heart attack. We developed these approaches for heart attack prevention through clinical trials. The RA community has learned from these approaches and similar prevention-type trials are now underway in RA."

"Most autoimmune diseases are only identified once an individual gets 'sick.' For example, with RA, once someone has painful, swollen joints," adds Dr. Cheung. "Blood-based tests can now identify individuals who are at risk before they feel sick, opening a whole new world of screening and possible prevention. Treating RA very early may allow for cheaper, safer therapies to work because once full-blown RA has developed, typically very powerful medications are needed to control disease."

In a Commentary on the clinical burden of RA, John M. Davis III, MD, MS, Associate Professor of Medicine, Division of Rheumatology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA, makes the case that preventive approaches would greatly benefit RA patients. "There have been great advances in the development of conventional synthetic, biologic, and targeted disease-modifying antirheumatic drugs (DMARDs) to treat RA as well as strategies to use these agents to

control disease-associated inflammation to the state of either low disease activity or clinical remission," he comments. "However, with any given treatment strategy, up to 40-60 percent of patients ultimately respond inadequately. Investment in developing preventive strategies is expected to lead eventually to a paradigm shift from treating disease and disease-related complications to maintaining health of people worldwide."

The rigorously peer-reviewed articles in this themed issue cover topics such as the natural history of RA; nomenclature for the stages of development of RA; potential pharmacological targets; potential for prevention by targeting mucosal processes; predicting RA in at-risk individuals; optimal trial design for RA prevention studies; patient preferences; regulatory considerations; system challenges; monitoring safety; and adverse events. All of the authors contributed in a significant way to the overall picture of how RA prevention is developing.

The issue identifies several important challenges:

- Getting society to invest in prevention, which requires that groups such as governments, the insurance industry, and pharmaceutical companies are also interested in prevention and willing to support it.
- Finding prevention approaches that work—whether drugs or lifestyle changes (e.g., smoking cessation), or combinations of both.
- Finding individuals who are at-risk for future RA through simple methods, which could be population-based blood testing or other approaches.
- Getting the research and medical community to agree on the right terminology for RA. "Right now, RA is only applied once someone has arthritis. But it may be that we need to develop new terms like 'Pre-RA' that can be used to identify someone at high risk for future RA. For example, the term pre-diabetes is

commonly used and is helpful for people to understand that they are in a stage of disease that indicates that they are at risk for getting worse unless they do something. We need similar terms in RA that can resonate with people, and help them take action," comments Dr. Deane.

- Patient preference is also a major challenge. "Asking at-risk individuals to take medications with possible side effects when there is no clinically apparent disease is not easy at all," observes Dr. Cheung.

Many other rheumatic and autoimmune diseases follow a similar model as RA where there are blood markers that are abnormal, sometimes years before an individual feels "sick" from disease. These diseases include lupus, gout, and others such as vasculitis.

"RA science is in a fortunate situation compared to many other inflammatory diseases where it is rarely known when and where disease-specific immunity may be triggered and how it may gradually evolve towards targeting of the end organ," comments Lars Klareskog, MD, Ph.D., Rheumatology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, in a Guest Editorial. "Research and solutions proposed in this issue may also serve as a demonstration example for many other chronic immune-mediated diseases."

Editor-in-Chief Richard Shader, MD, Tufts University School of Medicine, Boston, MA, USA comments, "The efforts of this team of experts to raise awareness of RA and to explore methods for early detection and intervention should catalyze the medical and scientific communities to increase their efforts to find better ways to treat and perhaps even prevent RA and its complications."

Prior research has already shown that the development of RA can be

delayed with a single dose of medication that is typically used in people who have full-blown RA. That finding suggests that if individuals can be identified at the right time, future RA can be delayed or completely prevented. There are also multiple clinical trials underway that should help determine which drugs have the potential to prevent RA and who the best candidates are to receive this treatment.

"Treating RA very early may allow for cheaper, safer therapies to work because once full-blown RA has developed, typically very powerful medications are needed to control the disease. This is like stopping a fire when it is still at the stage of a candle—pretty easy. However, stopping a fire once a full-blow forest fire has developed is very hard!" conclude the Guest Editors.

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