Editorial

Rheumatoid Arthritis Prevention: Challenges and Opportunities to Change the Paradigm of Disease Management

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Rheumatoid arthritis (RA) is a common chronic inflammatory arthritis affecting ~1% of the general population worldwide.[1] In addition to chronic synovitis, persistent systemic inflammation and immune dysregulation in patients with RA are associated with other comorbidities, such as cardiovascular diseases, interstitial lung disease, and malignancies.[2]

Fortunately, our understanding of RA has evolved considerably during the past decade. One of the most important new discoveries is the recognition of key inflammatory cytokines in the pathogenesis of RA, which in turn led to the introduction of biologic therapies. The first biologic approved by the US Food and Drug Administration for use in the treatment of RA was anti–tumor necrosis factor α therapy, and now multiple anticytokine as well as other biologic therapies are available, including anti–interleukin-1/6 therapies, B-cell depletion, and co-stimulatory blockade.[3,4] These new biologic therapies, together with a better understanding of how to use conventional disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate) as well as other improvements in care, including finding and treating patients soon after the onset of synovitis[5] and treat-to-target approaches,[6] have significantly improved the lives of patients with RA. Indeed, it is now possible to achieve disease remission on drugs, tapering of drugs,[7] and potentially even drug-free remission in some patients with RA.[8]

However, despite these advances, RA still has a significant negative impact on quality of life and productivity as well as health care costs.[9] Furthermore, even with current therapies and the increasing potential to taper therapy and achieve drug-free remission in some patients, for most people with RA, and especially autoantibody-positive RA, it is a lifelong disease for which patients will require some form of therapy for life to maintain adequate sustained control of the disease. In addition, while mortality in RA has improved,[10] many studies suggest that it is still higher relative to those in non-RA populations.[11,12] Finally, while early treatment is a known benefit in RA, it is difficult to implement, as lag times between the onset of symptoms and the initiation of DMARD therapy exceed 12 months in many areas of the world.[13–15]

As such, it is an important goal to implement interventions during a period of disease development when there are high-risk features (eg, family risk, environmental exposures, or abnormal biomarkers such as autoantibodies) but prior to the first clinical appearance of synovitis. This period may be termed a "window of opportunity," when interventions may lead to a permanent improvement in the immune system that in turn reduces the future development of joint disease or other aspects of RA, such as lung disease and cardiovascular disease. In addition, targeting this window may allow for less powerful interventions to still have a beneficial effect, because immune system abnormalities may not yet have progressed to significant dysregulation, and therefore the abnormalities are more easily improved.

Notably, this approach is difficult to fit into the "classic" paradigm of primary, secondary, and tertiary prevention: These phases become difficult to identify as the understanding of the development of this disease evolves,

and biomarkers and other factors are now used to identify patients who have abnormalities in some features of their health prior to any clinically apparent manifestations of disease. In RA in particular, disease is currently defined as clinically apparent synovitis that meets established classification criteria such as the 1987 American College of Rheumatology criteria[16] or the 2010 American College of Rheumatology/European League Against Rheumatism criteria,[17] although in some cases treatment is initiated if there is synovitis in the absence of fulfillment of the criteria. As such, as our understanding of the disease evolves, we may be able to better apply terms such as *primary, secondary,* and *tertiary prevention* in RA. Regardless, however, the identification of patients in a phase of RA development in which significant tissue damage has not occurred may lead to improved lives of patients who are at risk for RA, as well as potentially reduce the costs associated with this disease.

In terms of moving toward "preventive" approaches in RA that can be implemented prior to the onset of clinically apparent synovitis, in parallel to identifying new therapies for RA, we have also extended our understanding of the pathogenesis and timing of the development of RA. In particular, a number of studies have demonstrated that combinations of serum elevations in antibodies to citrullinated protein/peptide antigens and rheumatoid factor, as well as newer antibody systems (eg, anti–carbamylated protein antibodies), can be present for years prior to the first clinically apparent synovitis, a period that can be termed "pre-RA."[18–21]

These observations, as well as those from other studies that have demonstrated that there can be increasing joint symptoms in pre-RA, have underpinned the development of several clinical trials of strategies designed to prevent the onset of clinically apparent synovitis in high-risk patients who at this time are identified and defined by the presence of high-risk biomarkers and joint symptoms yet in absence of signs of clinically apparent synovitis.[22]

The results from 2 of these studies have been published. In one, the use of 2 doses of the corticosteroid dexamethasone did not halt the development of clinically apparent synovitis in antibodies to citrullinated protein/peptide antigen–positive and/or rheumatoid factor–positive patients, although there were statistically-significant reductions in autoantibody levels in treated individuals.[23] In the other study, the PRAIRI (Effects of B-Cell Directed Therapy on the Preclinical Stage of Rheumatoid Arthritis) trial,[24] a single dose of rituximab (1000 mg) did not significantly reduce the overall progression to synovitis, although it did result in a significant delay in its onset.

Importantly, these trials, along with other studies that have demonstrated that the initiation of DMARD therapy soon after the onset of clinically apparent synovitis results in better long-term outcomes, have kept hope high that prevention in RA may be viable. As such, several ongoing studies are evaluating the role of several agents, including hydroxychloroquine, abatacept, methotrexate, and statins, in prevention.[25–28]

The results from these ongoing trials will be highly informative to the field, and may lead to a paradigm shift in which prevention is a major part of how we approach RA—much like prevention is integrated into many other diseases, such as cardiovascular disease, metabolic bone disease, and cancer. However, in addition to opportunities for improving disease outcomes and costs, moving a field into the prevention realm has many challenges.

These challenges include carefully understanding the current state of RA in terms of diagnosis and management, morbidity and mortality, and financial costs so that the potential costs and benefits of prevention can be seen in that light.[29,30] Universally accepted nomenclature about the stages of RA development needs to be established to harmonize prevention as well as to make RA easier to describe to clinicians and laypeople alike.[31] While current models that include autoantibodies, symptoms, and other factors are fairly accurate in predicting future RA, these models need to be refined and made more accurate; furthermore, infrastructure needs to be developed to screen and identify patients at high risk for RA so that these patients can be enrolled in trials.[32] We will also have to sufficiently understand the pathophysiology of RA to target the right pathways and processes for effective prevention.[33] These interventions can include pharmacologic as well as lifestyle interventions, such as smoking cessation or improvement in obesity—both factors that have been reproducibly associated with a higher risk for future RA.[34–37] Indeed, it may be that, for prevention, very different pathways are targeted than in established RA. Following this, the emerging role of the mucosal inflammation and the microbiome in triggering and propagating RA-related autoimmunity may play a key role in prevention in the future.[38,39] Furthermore, these interventions will need to be implemented in well-designed trials that have meaningful clinical as well as biological outcomes.[40] Given that prevention will target patients who may not feel all that ill, in order to enroll and complete prevention trials, it will be critically important to understand patients' preferences for participating in prevention.[41] The safety and regulatory aspects surrounding prevention will also need

to be well understood and integrated into trials and ultimately clinical preventive care.[42–44] Finally, financial models will need to be developed that demonstrate the cost-effectiveness of identifying at-risk patients and then implementing prevention. Prevention will also have to be seen as a viable model in the emerging future of medicine and especially in an era when specialist rheumatologic care is becoming more difficult to access in many areas of the world.[14,27,45]

For this themed issue of *Clinical Therapeutics*, a number of experts in the field initially met as a working group to identify the major areas relevant to prevention in RA. Following that, a panel of experts was selected to write articles that address each of these areas. The final product is this themed issue, the overall goal of which was to provide a comprehensive discussion of the issues surrounding RA prevention that may also have applicability to other rheumatic conditions, including systemic lupus erythematosus, hopefully moving the field closer to prevention as a viable part of the care for patients with RA.

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