Commentary

Preventing Rheumatoid Arthritis: A Global Challenge

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ABSTRACT

Significant advancements have been made in the discovery of gene signatures, biomarkers, novel therapeutic targets, diagnostic tools, and risk factors that predict the development of rheumatoid arthritis (RA). There is also overwhelming evidence that treatment of early RA can prevent or alter disease progression and potentially lead to drug-free remission. Despite these advancements, there are significant challenges to identifying patients at risk of developing RA on a global scale. This commentary provides an overview of challenges related to the primary, secondary, and tertiary prevention of RA in the context of health care systems. Patient-level, provider-level, and health care system–level barriers to implementing prevention strategies are discussed. Strategies and opportunities to address these challenges, on both a local and global scale, are reported. Benefits as well as potential negative consequences that may be associated with implementation of prevention strategies for RA are discussed in the context of individuals and public health. (*Clin Ther*. 2019;41:1355–1365) © 2019 Published by Elsevier Inc.

Key Words: access to care, preclinical disease, prevention, rheumatoid arthritis.

INTRODUCTION

Significant advancements have been made in the discovery of gene signatures,[1] biomarkers,[2–5] novel therapeutic targets,[6] diagnostic tools,[7–10] and risk factors[11–17] that predict the development of rheumatoid arthritis (RA). Several therapeutic strategies and recommendations[18,19] for the treatment of RA can facilitate optimal care for patients with a better prognosis than that observed historically. The emphasis is now on early intervention with the aim of altering the natural history of RA by preventing or reducing irreversible joint damage.[20–22] In the early stages of RA development, there exists a period when the immune dysregulation is potentially reversible. This period has been termed the "window of opportunity" during which therapy may have the capability to alter the disease process and influence its long-term disease progression.[22]

Despite these advances made over the past 2 decades, there are many challenges and uncertainties surrounding our ability to shift the paradigm of care from optimizing care management of RA toward disease prevention. This commentary provides an overview of challenges related to the prevention of RA, and potential strategies and opportunities to address these challenges.

CHALLENGES IN QUANTIFYING AND IDENTIFYING RISK OF RA

One prerequisite to inform preventive strategies for RA is the ability to adequately estimate the population-level risk as well as an individual's risk.[23] There is a plethora of evidence surrounding estimates of RA incidence and prevalence globally, providing valuable public health information regarding the burden of disease at the population level. Geoepidemiologic differences in the incidence of RA worldwide exist,[24,25] with yearly incidence rates for RA appearing to be similar in North America and Northern Europe but generally lower incidence rates in southern Europe and the rest of the world.[26] These

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differences may be reflective of true variations based on underlying risks among different populations, or a reflection of different diagnostic care pathways in various settings. For instance, regions with a low incidence of RA may have many individuals left undiagnosed.

Moreover, the lifetime risk of developing RA varies between and within individuals and over time, and there are very few estimates of lifetime risk of RA available. In the United States, the lifetime risk of developing RA is 3.6% (1 in 28) for women and 1.7% (1 in 59) for men.[27] An individual's absolute risk may also be higher or lower than these estimates depending on other personal sets of risk factors.[28–30] For example, persons with a family history of RA in a first-degree relative have a 3 to 5 times higher risk of developing RA.[31] Thus, determination of an individual's risk factors is also a necessity in preventative strategies for RA.[23]

Individual disease prediction, risk assessment, and health risk appraisal tools have been established for many chronic diseases, and some of them have been adopted into clinical practice guidelines and recommendations.[32–34] Unfortunately, accurate methods of predicting those at high risk for future RA are not well established.[35–38] Knowing an individual's predicted risk increases their awareness of their chronic disease and the importance of prevention, helps to communicate their risk, and motivates lifestyle modifications or adherence to care management.[39] Numerous studies have been undertaken to understand distinct risk factors for RA.[28,35,40–43] Both environmental and genetic factors seem to be important in determining RA susceptibility, and it is likely that they interact.[44–46] Risk calculators are based on the notion that multiple risk factors may interact to increase the risk of developing a disease such that individuals with modest increases in several risk factors may be at an equivalent or higher risk of disease than individuals with only one highly elevated risk factor. Accurate RA prediction models that account for the constellation of risk factors are needed to optimize preventive strategies.

In addition, most patients who develop RA will pass through several phases of increased risk. The phases include the following: (1) at risk on the basis of genetic and environmental risk factors; (2) at risk on the basis of laboratory abnormalities; (3) at risk on the basis of symptoms of inflammatory arthritis; (4) individuals with synovitis on imaging but no clinically apparent inflammatory arthritis; and (5) individuals with clinically apparent inflammatory arthritis not yet fulfilling the classification criteria of RA.[47] Preventive strategies to target modifiable risk factors may need to be implemented at several points through these various phases of increased risk, as well as before the development of asymptomatic disease (primary prevention), during asymptomatic disease (secondary prevention), and after clinically apparent disease has developed (tertiary prevention).[48] However, developing preventive strategies that target risk factor modification interventions in preclinical phases (before and during development of asymptomatic disease) are hampered by a comprehensive lack of understanding of the modifiable exposures that influence the development of RA.[35]

UNCERTAINTY SURROUNDING OPTIMAL SCREENING STRATEGIES FOR RA

Screening for at-risk individuals is an important part of preventive medicine. Its rationale is to identify disease during an early and presymptomatic stage. Early disease may be easier and less expensive to treat, which positions screening strategies as potentially sound investments for health care systems. Several countries have developed national screening programs for other conditions that have led to increased disease detection rates and prevention.[49–51]

When determining whether a screening test or program is worthwhile, some of the most important factors are evidence-based recommendations for screening, competing priorities, and testing errors.[52] Screening strategies also need to show cost-effectiveness and the ability to target subjects with the highest absolute risk. Unfortunately, objective tests do not suffice for screening for RA, and definitive studies of the effectiveness of screening programs for RA are currently not available. The inability to accurately estimate the population-level risk as well as an individual's risk adequately will also hamper our ability to assess the effectiveness of methods to screen populations in which targeted preventions for RA would be most beneficial.[35]

In terms of identifying individuals in phases before the development of RA, highly sensitive screening tools seem to be warranted given the amounting

evidence illustrating that the earlier treatment of RA, the better the outcome and the lower the burden of RA on health care systems and individuals.[35,53] However, screening tools also require sufficiently high positive predictive values (PPVs) for future disease that would allow for balancing risks for developing disease and the potential benefit of prevention against the risks of potential adverse effects from the test itself, including overdiagnosis, overtreatment, inappropriate health care utilization, and psychological, medical, and economic consequences that may result from false positivity.[48,54] Overscreening, overdiagnosis, and overtreatment have been shown to be problematic in other areas of medicine.[55–57]

Screening for autoantibodies among individuals at risk of RA on the basis of genetic and environmental risk factors with no symptoms or signs of inflammatory arthritis will unlikely result in better yield.[54] Although autoantibodies are known to be present before clinically apparent RA, and these tests have shown to have very high PPV and specificity,[8,58–60] when the diagnostic accuracy of these autoantibodies is compared with that of the general population, PPVs are dramatically lower.[58] Screening for autoantibodies would be very expensive given that the rate of positivity is 3%–4% in the general population.[61,62]

The development of high-quality, inexpensive genetic predictive tests for the assessment of RA risk will likely appear on the horizon.[63,64] Yet, with advances in genetic technology, the rate at which new disease genes are being identified is outpacing the ability of professionals and policy-makers to assess the potential benefits and pitfalls of introducing or expanding genetic screening programs.[65–69] Ultimately, the decisions to develop, implement, and fund genetic screening programs are political,[69,70] and efforts are generally targeted toward conditions more highly prevalent than RA.[71]

DELAYS TO APPROPRIATE CARE

In the absence of widespread screening interventions for the primary and secondary prevention of RA, physical symptoms are most often the trigger for an individual to seek care. Before RA is diagnosed, many patients present with undifferentiated inflammatory arthritis or with arthralgia.[72,73] Once clinically apparent disease has developed, there are several barriers impeding tertiary prevention strategies in most countries. These delays occur at the level of the patient (delay in help-seeking for symptoms), primary care provider (delays in referral from primary care), rheumatologist (delays in establishing a diagnosis and initiating treatment), and health care system (limited access to rheumatology specialty services). Barhamain et al[74] quantified the lag time to RA diagnosis using data from 37 studies. The lag between symptoms and first physician consultation was >3 months (range, 0–6 months), another 2-month delay (range, 1–7 months) occurred between the physician visit and referral to a rheumatologist, an additional 3 months (range, 0–5 months) to achieve diagnosis by a rheumatologist, and 2 months (range, 0–2 months) to initiate treatment. The median (range) lag time from symptom onset to therapy was 12 months (4–24 months) months. However, it is important to acknowledge that these studies quantified delays among patients who ultimately had an established RA diagnosis. Evidence regarding health care utilization among individuals transitioning through the various at-risk phases for RA[47] is not well defined. Studies among patients with undifferentiated inflammatory arthritis are heterogeneous, and not all patients will progress to chronic RA.[75] Approximately 40%–50% of patients with undifferentiated inflammatory arthritis experience spontaneous remission and ~30% develop RA.[76]

In general, patients face the greatest wait-related risk at the earlier stages of care before a disease has been fully characterized.[77] Patient self-awareness of the initial physical signs of RA is limited due to the variability of symptoms experienced during preclinical RA onset. In addition, factors that determine whether a person will seek care may vary. Help-seeking has been conceptualized as the process through which people decide if, when, and how they will use health services as part of their overall illness-management strategy within the context of the health care system and their daily lives. Factors that determined whether a person will seek care can vary and may include geographic location, patient and provider characteristics, and disease onset and presentation and its impact on functional ability, as well as cultural and health beliefs.[79] There has been an increasing emphasis on improving the health literacy of individuals to enhance the diagnostic and

management of chronic diseases. However, it has been suggested that these approaches have typically been one-sided and limiting and require a broader scope of health literacy.[80]

Additional potential facilitators to support earlier detection of RA at the patient level include community case-finding strategies, self-administered patient screening tools,[81–84] public awareness, and social media campaigns.[85] However, data to support the cost-effectiveness of these interventions are limited.[86] Although these activities are useful in raising awareness, enhancing health literacy, and motivating health-seeking behaviors, they may also facilitate inappropriate use of health care services.[87]

In most countries, family physicians are the gatekeepers to rheumatology care. Potential barriers at the primary care level include limited awareness of signs and symptoms of inflammatory arthritis and limited awareness of the urgency and benefits of treatment, as well as a perceived lack of access to rheumatology specialists.[88,89]

Primary care education programs and rapid access clinics are the most efficacious strategies for promoting early referral in primary care.[86] Because most family physicians are likely to see very few new cases of RA annually, their perceived learning needs may prioritize other more prevalent conditions. However, newer medical learning models such as the Extension of Community Healthcare Outcomes interprofessional model, which aims to create a supportive learning community for family physicians to enhance their skills and confidence in managing complex chronic conditions, is increasingly being shown to offer advantages over traditional training methods.[90–92]

In many countries, a traditional primary-care-to-rheumatologist referral process occurs in which new patients are referred directly to a specific rheumatologist.[93] Delays resulting from waiting to see a rheumatologist after a referral has been requested may be a consequence of poor availability of rheumatology services or poor communication, such as ineffective referral letters that lack pertinent information, resulting in the inability to effectively prioritize patients.[94–100] Studies have reported that up to 40% of rheumatology referrals (for other self-limiting conditions) are unneccessary,[93,101] which would enable rheumatologists to prioritize patients with RA to be seen more promptly. A key strategy for improving rheumatology access and care coordination has involved pre-appointment or triage management to reduce inappropriate referrals.[102,103] Guidelines for referral can also improve appropriateness of care by improving pre-referral investigation and treatment.[104] Also proven to be effective are rapid access clinics, interdisciplinary care teams, and tele-rheumatology that facilitate early assessment of appropriate patients and provide integrated care pathways that link primary and secondary care.[86,105–116]

Delays in establishing a diagnosis may persist even after seeing a rheumatologist. Although RA is still regarded as a single disorder, in the clinical setting, RA is a heterogeneous disease, and presently no diagnostic criteria exist. Although the 2010 RA classification criteria[117] offer higher sensitivity (at a cost of lower specificity) than the 1987 criteria,[118,119] these classification criteria are not synonymous with diagnostic criteria but rather maximizing homogeneous populations for research study purposes at the expense of excluding some patients with less common phenotypes.[120]

The diagnosis of RA has been hampered by the lack of a truly disease-specific serologic marker.[121] Although the presence of autoantibodies is considered an important characteristic of RA, approximately one third of patients with early RA lack these autoantibodies,[122] and variations in assays and test result interpretation have been reported.[123] Rheumatologists may also be faced with limited access to or affordability of testing in certain geographical regions, patients' own financial and/or insurance limitations, and patient preferences when deciding on testing for autoantibodies to aid in establishing a diagnosis.[120]

INCREASING CHALLENGES FACED BY HEALTH CARE SYSTEMS TO SUPPORT RA PREVENTION

Perhaps the greatest challenge of all is the lack of health services capacity to support primary, secondary, and tertiary prevention strategies for RA. Rheumatologist supply has not kept pace with the needs of the changing population growth and demographic variables and the resultant increasing burden of RA.[124–128] The World Forum on Rheumatic and Musculoskeletal Diseases identified reduced access to rheumatology services as a key barrier for effective management of rheumatic

diseases globally.[126] Comprehensive workforce studies have reported deficits in the number of rheumatologists that will be only amplified with time.[129,130] Reports have also identified that the clinical activity of rheumatologists may be declining[127,129] as a result of changing demographic characteristics of rheumatology workforces, including generational effects and increasing feminization.[127,131]

In other areas of medicine, similar challenges facing the prevention of other chronic diseases globally include limited funding and strained health human resources, little coordination of prevention efforts among disease-oriented programs, limited research opportunities, and the size of the population at risk.[132–134] These findings have broader implications for public health entities because they are attempting to implement similar prevention recommendations for multiple diseases.

TRANSLATIONAL DELAYS IMPEDING DISCOVERY RESEARCH TO PUBLIC BENEFIT

Translating scientific discoveries into patient benefit more quickly is a priority of many health care systems. During the next decade, basic and clinical scientists will hopefully develop high-quality, inexpensive predictive tools for the assessment of RA risk, as well as primary and secondary preventive therapies. However, until there is better understanding of the cause(s) of RA, development of cause-directed, curative therapies and preventive strategies is still severely hampered.[135] Even with tertiary prevention strategies involving current therapies, it remains unclear how therapies targeting different molecules achieve similar efficacies in clinical trials, and comparable effectiveness has also not been seen when new therapies are applied to real-world patient populations. Furthermore, it is frequently stated that it takes ~17–25 years for discovery research evidence to reach clinical practice at a rate of 50% use in the relevant population.[136,137] Greater precision in diagnostic and treatment pathways will hopefully expedite advancements in predicting optimal responses or toxic risk as newer treatments emerge. To develop personalized medicine strategies for preventing the development and progression of RA, the clinical and molecular properties of the individual patients still need to be well characterized.[138] In addition, maximizing precision medicine will also need to be informed by individual needs, as well as by population health imperatives of an early and accurate diagnosis, which is a necessity to best practice care.[139]

CONCLUSIONS

There is no question that RA is a serious and growing public health problem. Developing primary and secondary preventive strategies in RA would represent a significant paradigm shift from treatment to prevention and would have major implications for patients as well as society. Finding asymptomatic patients with preclinical RA is a desirable goal, but there are many obstacles to overcome in primary and secondary prevention efforts, and there may be potential negative consequences related to overscreening, overdiagnosis, and overtreatment. Moreover, despite successful tertiary preventive strategies in controlling disease progression, there remains a considerable unmet need in reducing the burden of RA globally.

CONFLICTS OF INTEREST

The author has indicated that she has no conflicts of interest regarding the content of this article.

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