Commentary

Extra-articular Manifestations and Comorbidity in Rheumatoid Arthritis: Potential Impact of Pre–Rheumatoid Arthritis Prevention

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ABSTRACT

Rheumatoid arthritis (RA) is associated with a wide variety of extra-articular manifestations and comorbidities, several of which can be organ- or even life-threatening. These extra-articular manifestations and comorbidities can also contribute to the physical disability and psychological morbidity of RA that lead to reduced quality of life, higher direct and indirect costs, and societal burden of the disease. Although the expansion of RA treatment options and adoption of treat-to-target approaches has reduced the incidence and severity of several nonarticular manifestations of RA, such as rheumatoid vasculitis and cardiovascular disease events, this does not seem to be shared by all RA comorbidities. Moreover, a number of highly prevalent and impactful RA-driven comorbidities, such as accelerated atherosclerosis, interstitial lung disease, and sarcopenia, can present clinically in the years before the manifestation of joint pain or observable synovitis. A larger proportion of patients with RA have atherosclerosis, myocardial dysfunction, interstitial lung disease, and sarcopenia that is subclinical in the preclinical and earliest clinical phases of RA, emphasizing the importance of targeting the pre-RA phase for the prevention of comorbidities that are often poorly responsive to treatment once they develop. Herein, we review the potential impact of pre-RA prevention on the incidence and burden of extra-articular manifestations and nonarticular comorbidities. (*Clin Ther*. 2019;41:1246) © 2019 Published by Elsevier Inc.

Key Words: cardiovascular disease, depression, disability, health care cost, quality of life, sarcopenia.

INTRODUCTION

Although rheumatoid arthritis (RA) is primarily considered a disease of synovium-containing joints, it can also directly or indirectly affect most of the organs and tissues of the body. These nonarticular features can occur in several forms. Although consensus is lacking on how to define nonarticular features and classify their severity, they can be broadly categorized as "extra-articular manifestations" (EAMs) and "comorbidities."[1] EAMs generally involve cellular infiltration of activated immune effector cells into affected tissues leading to structural damage and, potentially, organ dysfunction.[2] These can range in severity from nonsevere (eg, subcutaneous nodules) to severe and potentially life-threatening (eg, vasculitis, pachymeningitis, fulminant interstitial lung disease [ILD]). These can manifest suddenly with little or no subclinical period. More frequently, EAMs present more insidiously with a longer subclinical period, such as most forms of RA-associated ILD and the subclinical myocarditis of RA that may lead to progressive myocardial dysfunction. Prevalence estimates for EAMs vary across studies due to the type of RA population sampled, but a general range of 20%–40% of patients with RA were reported to have least one EAM and 1%–20% were reported to have a severe EAM.[2,3]

A variety of risk factors for EAMs have been reported and are not consistent across all studies. However, the most frequent are seropositivity (rheumatoid factor [RF] and anti–cyclic citrullinated

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antibodies in most reports but also antinuclear antibody positivity), smoking, and possibly male sex.[2,4] In addition, EAMs can be observed as the cumulative effect of long-standing high articular disease activity, high levels of systemic inflammation, and undertreatment of articular disease. However, relevant to this review, most can be observed even in early RA (ie, the first few years of disease) and in the pre-RA period before articular symptoms have manifested.[5,6] They can also occur as the presenting manifestations of RA,[7,8] suggesting underlying mechanisms unrelated to chronic inflammatory burden.

In contrast to EAMs, RA-associated comorbidities are considered secondary to inflammatory burden and/or consequences of treatment. RA-associated constitutional symptoms, fatigue, infections, anemia, depression, and other psychosocial manifestations may be considered comorbidities and not strictly EAMs.[9] However, whether accelerated atherosclerosis, osteoporosis, and sarcopenic muscle loss are RA-associated comorbidities or EAMs has been debated.[2]

Regardless of classification, both EAMs and comorbidities have been associated with higher overall morbidity and mortality in RA. Any EAMs were associated with a >2-fold higher hazard of death in one study.[3] However, this association may be restricted to only those with severe EAMs.[10] Importantly, the risk of mortality associated with EAMs may not be directly related to the EAM itself but indirectly through other comorbidities occurring in RA patients with EAMs. For example, Turesson et al[11] reported a >3-fold higher hazard of first cardiovascular disease (CVD) events among those with severe EAMs compared with those without EAMs, an association that was not mediated by demographic characteristics, smoking, or seropositivity for RF.

EAMs and comorbidities also increase the direct and indirect medical and nonmedical costs associated with RA.[12] The economic burden of RA is already substantial, and the additional direct costs of RA EAMs and comorbidities, which include the added medical costs incurred for diagnosis, treatment, and monitoring, increase this burden.[13] The added costs of specific EAMs and RA-associated comorbidities are discussed in more detail in subsequent sections. Less studied are the indirect costs of EAMs and comorbidities in RA, which include work disability and loss of productivity by the RA patients and their caregivers over-and-above those related to their articular disease activity. These also include intangible costs related to the psychosocial impacts of EAMs and comorbidities, which contribute to depression and anxiety. Importantly, estimates of the economic burden of RA suggest that the indirect costs of RA are at least as great in magnitude compared with the direct costs and, depending how modeled, may exceed them.[13] This relationship likely extends to the incremental economic burden of EAMs and comorbidities.

Treatment of RA has changed dramatically over the past 2 decades, both in terms of the treatments available and how they are applied. Although there is clear evidence that aggressive RA therapy earlier in the disease has been associated with improved joint-related outcomes and some comorbidities, it is not yet clear whether this extends to all EAMs and comorbidities. For example, in one longitudinal cohort study,[3] the overall incidence of EAMs was not different for cohorts observed after the introduction of biologic agents compared with earlier cohorts. As an exception, the incidence of certain severe EAMS such as rheumatoid vasculitis has declined, as well as evidence that mortality from EAMs and comorbidities is lower in recent years.[3,14] However, it is unclear what abilities, if any, pharmacotherapies targeting the reduction in synovitis and prevention of articular erosion have in halting or reversing the progression of many high-impact comorbidities once they manifest, such as atherosclerosis, myocardial dysfunction, ILD, and sarcopenia. Indeed, some commonly used therapies in patients with RA, such as glucocorticoids and NSAIDs, may themselves contribute to certain RA comorbidities (eg, atherosclerosis).[15] Methotrexate and leflunomide are commonly withdrawn or withheld from patients with RA and ILD,[16] and tumor necrosis factor (TNF) inhibitors are contraindicated in patients with clinical heart failure.[17] There is even observational evidence for a higher rate of severe EAMs among patients with RA after initiation of treatment with TNF inhibitors,[4] and there is controversy about TNF inhibitors contributing to the progression of ILD.[18] However, these associations must be interpreted under the likely possibility of confounding by indication as a potential source of bias. Regardless of

attribution, given the lack of effective therapies for most RA comorbidities, a strong argument can be made for pre-RA prevention, should a preventive strategy exist, as a more effective way to reduce the burden of EAMs and comorbidities.

In this context, the present review considers the potential impact of pre-RA prevention on the burden of RA morbidity, mortality, and associated direct and indirect medical and nonmedical expenditures associated with several high-impact EAMs/comorbidities, with a particular emphasis on CVD, respiratory diseases, sarcopenia, and depression.

BURDEN OF CARDIOVASCULAR DISEASE IN RA AND IMPACT OF RA PREVENTION

There is a wealth of evidence supporting higher rates of coronary atherosclerotic events, clinical heart failure, and cerebrovascular accident events in patients with RA. On average across a range of studies, CVD mortality and myocardial infarction (MI) events were 50% higher in RA compared with non-RA comparative populations.[19,20] CVD is the largest contributor to the excess mortality of RA, estimated at 50%.[21] The morbidity burden of a survived CVD event is also substantial in RA, with impacts on physical function, emotional well-being, and quality of life (QOL). In the only detailed comparative study of resource utilization associated with CVD in RA, Joyce et al[22] queried US medical and pharmacy claims for >10,000 patients with RA and claims between 2001 and 2005 who were followed up for 12 months. They reported significantly higher rates of hospitalizations (both RA- and CVD-related) in RA patients with any CVD compared with those without CVD (27% vs 10% with at least 1 hospitalization, respectively), and the average length of hospitalization was >3-fold longer for the RA + CVD group (2.92 vs 0.85 days). Patients with RA and CVD also had more outpatient and emergency department visits and higher laboratory and radiology utilization. Interestingly, patients with RA and CVD underwent arthrocentesis more frequently compared with those with RA but without CVD, perhaps reflecting lower rates of NSAID and cyclooxygenase-2 inhibitor use that were observed in this group. As expected, use of CVD-related medications was more frequent in RA patients with CVD. However, use of non-CVD medications, including depression medications and narcotic analgesics, was also significantly higher in these patients, and there was greater use of corticosteroids. The adjusted 12-month mean total health care cost was 24% higher for the RA + CVD group compared with those with RA alone (US $14,100 vs US $11,300, respectively). Interestingly, RA-related costs were similar between the groups.

In addition to cost, comorbid CVD in RA can complicate treatment decisions. The entire class of TNF inhibitors is contraindicated in those with comorbid heart failure.[17] The use of NSAIDs and/or corticosteroids in patients with RA using anticoagulants for secondary CVD prevention or prevention of coronary stent thrombosis presents a safety risk.[23] In addition, it remains unclear whether increases in circulating lipid levels that can occur with treatment with inhibitors of interleukin-6 or Janus kinases are associated with CVD risk in RA patients with established comorbid CVD.[24] Although there is some evidence that TNF inhibitors and non-TNF biologic agents may reduce the incidence of CVD events in RA,[25,26] this scenario seems to be dependent on response[27] and is not certain for all agents.

Patients with RA are at risk for ischemic CVD events at all stages of disease, including the pre-RA period before articular disease has manifested. Maradit-Kremers et al[28] reported a >3-fold higher odds of hospitalized MI and an almost 6-fold higher odds of silent MI in the 2 years before fulfillment of clinical diagnostic criteria for RA. Despite a lack of articular disease activity during this period, potential contributors to atherogenesis/atherothrombosis are observed in patients with RA, including the propagation of autoimmunity (ie, epitope spreading of citrulline-targeted autoantibodies),[29,30] increasing levels of circulating inflammatory cytokines, chemokines, and proteinases,[30] and the atherogenic lipid profile of RA already observed before diagnosis.[31] The observation of an association between RA-associated autoantibodies and coronary atherosclerosis and CVD events in people without RA[32] suggests a role for a pre-RA intervention targeting the propagation of autoimmunity.

Patients with RA are also at a heightened risk of CVD events in the earliest phases of their disease after articular disease has manifested. The most current assessment of ischemic CVD events in RA comes from a recent population-based cohort study

of patients newly diagnosed with RA that included the entire Swedish population. Among a population of patients with RA diagnosed in the period of availability of biologic agents and in the era of emphasis on treat-to-target, Holmqvist et al[33] observed ~2 to 3 more incident acute coronary syndrome events per 1000 person-years between patients with RA in the first year of diagnosed RA compared with the general population. This difference in incidence was similar to that observed in the patients with RA followed up for longer periods. Broadly applying these estimates to the known vital statistics of RA in the United States, where the incidence of RA is 40 per 100,000 persons per year,[34] a pre-RA intervention that was 100% effective would prevent 130,000 new cases of RA each year. Assuming the pre-RA intervention would eliminate the incremental contribution of RA on incident ischemic CVD in this population, 260 to 390 ischemic CVD events would be eliminated in just the first year after RA diagnosis. The direct medical costs of an MI are estimated at approximately US $30,000 in the first year.[35] Assuming this estimate applies equally to the RA population, pre-RA intervention would save US $7.8 to $11.7 million for only the incident cases in the first years of RA diagnosis. Additional savings in indirect costs and the intangible burden of associated comorbidity associated with having RA and CVD would add to this saving.

BURDEN OF RESPIRATORY DISEASE IN RA AND IMPACT OF RA PREVENTION

RA can affect all of the structures of the lungs, including the airways, pleura, vasculature, and parenchyma.[36] Parenchymal involvement, in the form of RA-associated ILD, has the largest impact on RA morbidity and mortality across the aggregate RA population.[37] RA-ILD is not a homogeneous entity but exists in several radiographic and histologic forms that may reflect differing pathogeneses and may confer different implications for mortality.[38] Considering all of the subtypes together, when associated with clinical symptoms such as cough, dyspnea, exercise intolerance, and/or measured impairment of oxygenation, RA-ILD is associated with substantial morbidity and early mortality. Bongartz et al[37] reported that ~8% of patients with RA in a single-center sample developed symptomatic ILD over the course of their disease, and the median survival was only 2.6 years after RA-ILD diagnosis. Importantly, 25% died in the first year after diagnosis, and RA-ILD accounted for 13% of the excess mortality of RA. Using a larger sample of insurance claims data, Raimundo et al[39] reported an annual incidence of 2.7−3.8 cases of RA-ILD per 100,000 persons in the entire population (RA and non-RA). Thus, given the current US population of 325 million persons, 8775 to 12,350 new cases of RA-ILD would be estimated yearly. Median survival was 7.8 years after ILD diagnosis in the study by Raimundo et al, longer than that reported by Bongartz et al but still less than expected for a similar RA patient without ILD.

There is little research about the additional comorbidity burden of RA-ILD over that of RA alone. However, it is likely comparable with idiopathic pulmonary fibrosis (IPF), with which it shares many features. IPF can induce several potentially severe additional comorbid diseases such as pulmonary hypertension leading to heart failure, obstructive sleep apnea, and accelerated atherosclerosis.[40] IPF is also associated with markedly higher rates of depression, fatigue, and reduced QOL, which are observed in proportion to the severity of the underlying lung disease.[41] Both IPF and RA-ILD are associated with physical function impairment and the potential for work disability. RA-ILD is associated with higher direct health care costs due to increased health care utilization, inpatient admissions, outpatient office visits, emergency department visits, and diagnostic testing compared with RA alone. In one survey,[39] the incremental increase in direct health care costs of RA-ILD was US $28,000 to$32,000 per year, with the highest costs occurring in the first years after RA-ILD diagnosis.

Clinical RA-ILD presents challenges for the selection of disease-modifying antirheumatic drugs for the treatment of synovitis in patients with RA. The 2008 American College of Rheumatology RA treatment guideline recommended that methotrexate not be used in the setting of RA-ILD,[16] although this recommendation was not included in the 2015 update.[42] Case reports and small observational studies of worsening of RA-ILD in patients treated with TNF inhibitors[18] have led to increasingly cautious use of this biologic class in patients with RA-ILD. Importantly, ILD incidence and frequency

of exacerbation were not shown to differ for those patients prescribed TNF inhibitors compared with those prescribed other biologic agents such as abatacept, rituximab, and tocilizumab.[43] Patients with RA-ILD are exposed to higher cumulative doses of corticosteroids, which carry additional well-recognized risks and potential for comorbidity. Finally, immunomodulators frequently used in the management of certain forms of ILD are not effective for treating synovitis (ie, mycophenolate)[44] or are not first-line choices (ie, azathioprine),[42] and combining additional immunomodulators with these to treat both joint and lung manifestations may be associated with additional risk, particularly for infections.

Smoking, both current and former, is a well-supported risk factor for RA-ILD, and cumulative smoking was more potently associated with pulmonary fibrotic features in patients with RA compared with non-RA control subjects who were otherwise similar in demographic characteristics and total pack-years of smoking exposure.[45] A strong association of anti–citrullinated protein antibodies (ACPAs) with RA-ILD has also been shown in multiple studies,[46] an association strengthened by a history of smoking exposure. Longer disease duration is also a risk factor for RA-ILD. However, multiple studies have identified ILD occurring before the diagnosis of RA in up to 15% of cases,[47] and a simultaneous diagnosis of RA-ILD with RA was noted in 34%. This finding is not surprising, as ACPAs are observed years before the diagnosis of RA,[30] and ACPAs can be observed in patients with idiopathic ILD who never develop articular manifestations that are diagnostically consistent with RA.[48] Importantly, mortality was higher among patients with RA diagnosed with ILD before their RA diagnosis.[47]

Taken together, a pre-RA intervention that prevented or reduced the development of clinical ILD would result in reduced ILD-associated mortality, morbidity, and cost. Considering the yearly incidence of ILD (8775–12,350 new cases per year)[39] and the very high average direct cost incurred over the first 5 years after RA-ILD diagnosis (US $173,405 per patient),[39] a pre-RA intervention that was 100% effective would result in an estimated cost saving of a staggering US $1.3 to $1.9 billion over 5 years due to the high cost of treating clinical RA-ILD. Additional savings would result from the prevention of associated comorbidities and the intangible costs of the disease. Notably, these savings are greater than those of preventing CVD in RA. Because there are currently no effective treatments for RA-ILD, a preventive strategy would be ideal.

Assuming a preventive strategy was available, identifying the at-risk individuals to target before the development of clinical lung or articular manifestation would be challenging. Possible interventions could include smoking cessation in ACPA-positive individuals without manifestations of RA or ILD. Combined with this approach, an immunomodulator targeting the underlying pathophysiologic mechanisms that trigger ILD could be used. However, little is currently known about the exact mechanisms leading to RA-ILD in the pre-RA phase, and they may differ depending on the ILD subtype (ie, predominant patterns of usual vs nonspecific interstitial pneumonitis). It is also not clear whether the immunopathologic mechanisms that lead to RA synovitis are the same as those that predispose to ILD. Thus, it is possible that an effective strategy developed to prevent the articular manifestations of RA might have no effect on preventing RA-ILD and that such individuals could develop ILD without the articular manifestations of RA. Regardless, the potential to reduce or eliminate the burden of suffering and enormous cost of RA-ILD, coupled with the lack of treatment options once manifested clinically, make ILD the RA EAM most deserving of a pre-RA preventive intervention.

BURDEN OF SARCOPENIA IN RA AND IMPACT OF RA PREVENTION

Skeletal muscle catabolism occurring in the setting of acute and chronic systemic inflammation is termed sarcopenia.[49] Among a cohort of RA patients with both early and established disease,[50] >1 in 4 patients with RA (26%) met age-, sex-, and race-based criteria for sarcopenia measured by using dual-energy X-ray absorptiometry, a prevalence that was double that of age- and sex-matched non-RA control subjects. In that study, sarcopenia was observed with the same frequency among RA patients with earlier disease (<3 years) compared with those with longer disease duration, suggesting that sarcopenia is an early occurrence in RA. Low muscle mass was also observed in an inception cohort of RA patients with disease duration of <1 year,[51] suggesting that

preclinical immunologic events, such as the elevated levels of circulating inflammatory cytokines known before the onset of articular manifestations,[30] may already have deleterious effects on muscle. There is limited evidence to suggest that pharmacotherapies have the ability to reverse sarcopenia once it has occurred[52] and none that have studied RA directly.

Sarcopenia in RA is associated with both lower muscle mass as well as a reduction in muscle quality,[53] which can be assessed by measuring the radiographic density of skeletal muscle via computed tomography scanning. Low-density muscle is characterized by greater amounts of both intercalated and intramyocellular fat accumulation, resulting in impaired performance.[54] Both muscle mass and muscle density were highly associated with subjective and objective physical function in patients with RA,[53] with an impact as large as or even larger than that of articular disease activity and erosive joint damage. Sarcopenia predicts future mobility impairment, falls, fractures,[55] and mortality[56] in the general population, and low body mass index, a surrogate for sarcopenia, was associated with both overall[57] and CVD[58] mortality in RA. Low muscle mass and density in RA were also associated with impairment in valued life activities,[53] an assessment of how RA affects individuals' ability to participate in activities that are meaningful for them that are not captured by commonly utilized physical function assessments in RA (eg, the Health Assessment Questionnaire Disability Index [HAQ-DI]). The inability to participate in these meaningful activities likely has unmeasured consequences on QOL and emotional well-being.[59]

Considering the difference in prevalence of sarcopenia between RA and non-RA matched control subjects (13%) and the estimated prevalence of RA in the United States (1.3 million cases), one can project that there are ~169,000 individuals with sarcopenia that is attributable to their RA. Patients with RA and sarcopenia had a HAQ-DI score that was 0.25 unit higher, on average, than those without sarcopenia (1.0 vs 0.75 unit).[50] This difference in HAQ-DI score was associated with higher health care utilization and lower QOL in a study conducted in Australia,[60] which would correspond to a difference in yearly nonmedication medical costs of $3932 dollars (2010 Australian dollars). The added costs were incurred due to more office visits, hospital admissions, surgery, and RA-associated home modifications. Adjusting 2010 Australian dollars to 2018 US dollars,[61] the yearly direct medical expenditure due to the impact of sarcopenia on disability would be estimated at US $562 million for the 169,000 US patients with RA estimated to be sarcopenic, provided that medical costs related to RA disability are comparable between patients with RA in the United States compared with Australia. As with the economic estimates described in other sections, the indirect medical costs, nonmedical costs, and intangible costs are likely higher. Taken together, a pre-RA intervention that was able to prevent or reduce the development of sarcopenia would result in considerable improvement in physical function, QOL, and direct and indirect cost savings.

BURDEN OF DEPRESSION IN RA AND IMPACT OF RA PREVENTION

Depression is highly prevalent among patients with RA, with 13%−20% estimated to have depressive symptoms sufficient to meet clinical criteria for depression.[62] The incidence of depression and anxiety disorders is higher for patients with RA compared with matched control subjects. In a Canadian population-based survey,[63] RA was associated with an excess incidence of 7 per 1000 person-years for depression and 5 per 1000 person-years for anxiety disorders over-and-above the background non-RA population. Depression has been linked to a number of adverse health outcomes in RA, including lower QOL, reduced response to disease-modifying antirheumatic drugs, CVD, and higher mortality.[22,64,65] Presumably, a major driver of depression and other psychological comorbidity in patients with RA is persistent joint pain, disability, fatigue, and the presence of other nonarticular comorbidities and EAMs combined with background personality traits and the stress of dealing with the uncertainties of a chronic disease and its management. However, there is an emerging literature linking chronic anxiety and depression to areas of the brain involved in immune regulation,[66] such that chronic depression and anxiety themselves may contribute to the pathways that drive systemic and articular inflammation in RA.

Medical resource utilization is higher for patients with RA and depression. Compared with RA patients without depression, depressed patients with RA had

more total comorbidities, hospital admissions, RA-related surgery, arthrocentesis, and EAMs.[22] Emergency department visits were 3-fold higher for depressed versus nondepressed RA patients, and use of narcotics and corticosteroids was also higher for patients with RA and depression. On average, adjusted mean yearly health care costs were US $821 higher for RA + depression compared with RA alone (2006 dollars). Using these estimates and considering the excess in incident depression due to RA (7 cases per 1000 person-years),[63] a pre-RA intervention for RA that reduced the development of depression and anxiety would result in 9100 fewer cases of depression yearly. This approach would result in cost savings in direct medical expenditure of an estimated US $9.4 million (2018 dollars), with indirect, nonmedical, and intangible costs likely several times higher.

CONCLUSIONS

RA is a multisystem disease with multiple serious and potentially life-threatening nonarticular manifestations that affect physical functioning, emotional well-being, and overall QOL. Four of the most prominent RA EAMs/comorbidities (accelerated CVD, ILD, sarcopenic muscle loss, and depression) are associated with a significant added burden to physical and emotional well-being and increase the already substantial economic burden of RA. Many of these are observable in the early and pre-RA phases and are challenging to treat once they have developed. As such, an approach focused on pre-RA prevention would result in a reduction in the personal and societal burden of RA-associated EAMs and comorbidities. Because of this high burden, once inflammatory arthritis and classifiable RA have developed, the ability to prevent EAMs and comorbidities is a management goal equal to the ability to reduce articular signs and symptoms.

CONFLICTS OF INTEREST

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

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