Burden of disease in treated rheumatoid arthritis patients: Going beyond the joint

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\begin{abstract}
Objective: The disease burden in rheumatoid arthritis (RA) extends beyond the joint. This article evaluates the physical and psychosocial extra-articular burden of treated RA and relationships among diverse disease manifestations.

Methods: MEDLINE searches identified papers published in English from January 2003 to December 2012 that evaluated systemic complications and psychosocial aspects associated with RA. Preference was given to studies with randomized cohorts and large (>100) sample sizes. Of 378 articles identified in the initial search, 118 were selected for inclusion.

Results: RA is associated with multiple comorbidities and psychosocial impairments, including cardiovascular disease, osteoporosis, interstitial lung disease, infection, malignancies, fatigue, depression, cognitive dysfunction, reduced work performance, work disability, and decreased health-related quality of life. The etiology of the extra-articular burden may reflect the systemic inflammation and immune system alteration associated with RA, metabolic imbalances and side effects related to treatment, or the influence of comorbidities. Strategies that may help to reduce the extra-articular disease burden include personalized medicine and the potential introduction of treatments with new mechanisms of action.

Conclusion: Despite improvements in treating joint disease, the extra-articular burden in RA remains substantial, encompassing multiple comorbidities and psychosocial impairments.

\end{abstract}

Introduction

Rheumatoid arthritis (RA) is an inflammatory, immune-mediated disease with a prevalence of 0.5–1% in developed countries \cite{1,2}. In RA, chronic synovial inflammation and hyperplasia drive articular destruction and bone erosion, leading to functional decline and disability \cite{3}. The treatment paradigm for RA has changed dramatically over the last 15 years, with more effective interventions introduced earlier to prevent joint damage and functional impairment. Current recommendations from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) provide algorithms for the use of synthetic disease-modifying antirheumatic drugs (DMARDs) and biologics \cite{4,5}. Pharmacotherapies are started at the time of RA diagnosis, with the goal of achieving clinical remission or, if that is not possible, low disease activity. Specific treatment choices are guided by disease activity and prognostic features.

With this therapeutic approach, most patients can be treated effectively, and bone and cartilage destruction can largely be prevented. Nevertheless, it is important to recognize that RA is a systemic disease and other disease manifestations may still be present even though joint damage has been controlled. Although in the past, the clinical understanding of disease burden emphasized destruction of the joints, now it must also focus on the systemic manifestations associated with RA, including comorbidities, psychosocial aspects, and health-related quality of life (HRQOL) impairments (Fig. 1).

Methods

To identify the extra-articular burden of RA, we initially listed systemic complications and psychosocial factors associated with...
the disease based on our clinical experience and then conducted literature searches on MEDLINE to identify relevant articles published in English from January 2003 to December 2012. Search terms included “rheumatoid arthritis” in combination with “cardiovascular,” “osteoporosis,” “lung,” “pulmonary,” “infection,” “cancer,” “malignancy,” “fatigue,” “depression,” “cognition,” “cognitive dysfunction,” “quality of life,” “work performance,” or “disability.” Preference was given to articles describing clinical studies with randomized cohorts and large (> 100) sample sizes. Of 378 references identified by the initial search, 118 provided relevant clinical or epidemiologic data and were selected for inclusion. References identified by MEDLINE were supplemented by reviewing reference lists in selected articles and by abstracts presented at recent rheumatology meetings.

Results

Systemic comorbidities

Cardiovascular disease

RA patients have an approximately 2-fold higher cardiovascular risk compared with the general population [6]. Some traditional cardiovascular risk factors are more common in RA cohorts than in controls, including insulin resistance [7], altered fat distribution [8], cigarette smoking [7], and physical inactivity [9]. Other traditional risk factors, including dyslipidemia, hypertension, and diabetes, may also be more common in RA, but the evidence is less clear [10–13]. Nevertheless, the higher prevalence and clustering of traditional risk factors do not appear sufficient to explain all the excess cardiovascular risk [14,15]. The additional cardiovascular risk in RA likely depends on high-grade systemic inflammation interacting with traditional as well as nontraditional risk factors.

The excess cardiovascular risk is present in early RA and increases with longer disease duration [16]. Studies have found evidence of endothelial dysfunction as measured by impaired brachial artery vasodilation [17] and subclinical atherosclerosis as measured by increased carotid artery intima–media thickness and carotid plaque within the first year following RA diagnosis [17,18]. Although vascular function and morphology may be impaired in RA compared with the general population, many studies have been unable to find associations between systemic inflammation and these vascular changes [19]. RA patients who are asymptomatic for cardiovascular disease also have increased rates of pericardial and cardiac valvular involvement [20,21].

Epidemiological data suggest that RA confers a risk of myocardial infarction similar to that with diabetes [22], and observational studies show similar subclinical atherosclerotic activity in the 2 disorders [23,24]. Accordingly, RA may be considered as a coronary heart disease risk-equivalent disorder [25]. Importantly, cardiovascular risk prediction tools developed in the general population, such as the Framingham Risk Score, may underestimate the
cardiovascular risk in RA patients [26]. These prediction tools do not take nontraditional risk factors into consideration, including RA disease activity, rheumatoid factor positivity, radiographic joint damage, and glucocorticoid use, all of which may contribute to cardiovascular risk [27]. Because of this limitation, EULAR recommends multiplying the Framingham Risk Score by 1.5 in RA patients with disease duration > 10 years, seropositivity, or extra-articular manifestations [6]. Taken together, these observations underscore the importance of aggressive control of inflammation and management of dyslipidemia and other traditional cardiovascular risk factors in RA patients.

Substantial evidence exists to support a cardioprotective effect of methotrexate in patients with RA. Treatment with methotrexate is associated with reduction in the risks for acute myocardial infarction [28], congestive heart failure [29], and stroke [28]. The reduction in cardiovascular events translates into a decreased likelihood of mortality. A prospective cohort study of 1240 RA patients found a 70% reduction in the risk of cardiovascular death with the use of methotrexate compared to the non-use of DMARDs [30]. Few data exist to elucidate the potential mechanisms underlying these benefits. It has been hypothesized that the systemic anti-inflammatory effects of methotrexate, including downregulation of proinflammatory cytokines known to play a role in atherogenesis, may explain the reduced risk [31].

Clinical trials have shown the benefits of tumor necrosis factor (TNF) inhibitors and other biologics in slowing or preventing progressive joint damage, but these trials were not sufficiently powered to detect changes in comorbid cardiovascular risk [32,33]. A number of observational registries and meta-analyses indicate that TNF inhibitor therapy may reduce cardiovascular risk, with resulting decreases in major cardiovascular events, myocardial infarction, and stroke [32–34]. Other studies suggest that the cardiovascular risk reduction with TNF inhibitors may be confined to patients who respond to these agents [35] and may not differ substantially from the benefit seen with prolonged use of conventional DMARDs [28,36]. The exact mechanisms by which biologic and conventional DMARDs as well as glucocorticoids may affect cardiovascular risk are multiple and remain largely unresolved. Beneficial effects of anti-TNF therapy on blood pressure control [37], possibly by reducing systemic vascular resistance [38], have been described, whereas the opposite has been shown for long-term glucocorticoid therapy [39]. Effects of anti-TNF therapy and glucocorticoid therapy on lipid and insulin metabolism, as well as on body composition, appear far more complex [7,10,11,40–43], as are the effects on vascular function and morphology [19].

**Osteoporosis**

RA is associated with systemic bone loss and increased fracture risk, likely reflecting contributions from multiple factors, including disease activity, physical inactivity, and glucocorticoid use. In the British General Practice Database of > 30,000 RA patients, the risk of hip fracture was increased by 2.0-fold and vertebral fracture by 2.4-fold relative to non-RA controls [44]. In the RA cohort, disease duration > 10 years, low body mass index, and use of oral glucocorticoids were independently associated with increased hip fracture risk. In the Consortium of Rheumatology Researchers of North America (CORRONA) registry, which included 8419 female RA patients, postmenopausal status, higher modified Health Assessment Questionnaire (mHAQ) score, and glucocorticoid use were associated with higher overall fracture risk [45].

Systemic inflammation, measured by high-sensitivity C-reactive protein (hs-CRP) levels, has been associated with fracture risk in healthy cohorts [46,47]. Mechanistically, proinflammatory cytokines produced by the rheumatoid synovium, including TNF, interleukin (IL)-1, IL-6, and IL-17, can directly or indirectly upregulate the expression of the receptor activator of nuclear factor-κB (RANKL), a cytokine that is essential for the differentiation and activation of osteoclasts leading to bone resorption [48]. Inflammation present in synovial joints may also inhibit Wnt signaling, leading to reduced osteoblast function and inhibition of bone formation [48]. Consistent with the role of systemic inflammation in osteoporosis, the use of TNF inhibitors was associated with reduced fracture risk in the CORRONA registry [45]. Moreover, several case series, as well as an analysis of the phase 3 Efficacy and Safety of Adalimumab and Methotrexate (MTX) Versus MTX Monotherapy in Subjects With Early Rheumatoid Arthritis (PREMIER) study, suggest that TNF inhibitors may slow bone loss in RA [49,50].

The cause of ILD in RA is unknown, although DMARDs, TNF inhibitors, and glucocorticoids have been associated with it [57–60]. Despite the apparent absence of pulmonary toxicity with TNF blockers in large randomized clinical trials, new-onset ILD or exacerbation of preexisting ILD with high mortality has been reported in 144 RA patients following the use of TNF blockers [61]. Marked follicular B-cell hyperplasia has been detected in RA-associated interstitial pneumonia [62]. This suggests that rituximab, which targets CD20 to deplete B cells, may be useful in treating both RA and associated ILD [63]. However, rituximab has also been associated with new-onset ILD in isolated patients with RA [61]. Other morphological assessments show that mast cells and CD4+ cells are also prominent in RA-associated interstitial pneumonitis [64,65]. Both cell types are important in the rheumatoid synovium, and therefore it may also be therapeutically feasible to target these cells or their products against both joint and lung diseases in RA.

**Respiratory disease**

Interstitial lung abnormalities are commonly observed in RA, even in patients with early disease who have no respiratory symptoms. On high-resolution computed tomography (HRCT) of 126 RA patients, the most frequently observed abnormalities were bronchial dilatation (41%), ground-glass attenuation (27%), parenchymal micronodules (15%), subpleural micronodules (15%), reticulation (12%), and bronchial wall thickening (12%) [55]. Measures of small airway disease, including parenchymal micronodules and bronchial wall thickening, were more prominent in patients with long-standing RA than with early RA, whereas there was no difference between these subgroups in the frequency of interstitial abnormalities such as ground-glass attenuation and reticulation.

The lifetime risk of developing interstitial lung disease (ILD) is substantially higher in RA patients than in those without RA, as illustrated by a recent population-based study [56]. An inception cohort of 582 RA patients was followed for a mean of 16.4 years and compared with a matched cohort of 603 controls. The cumulative 30-year risk of ILD in these respective groups was 7.7% and 0.9%, which translated into a hazard ratio of 8.96 (95% CI, 4.02–19.94). The risk of developing ILD was associated with older age at time of RA onset, male gender, and greater RA disease severity. Moreover, RA patients who developed ILD had a 3-fold increase in mortality compared with RA patients without ILD.

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Given the risk of osteoporosis and its potential adverse impact on outcomes, it is important for at-risk RA patients to undergo regular monitoring of bone mineral density and to receive calcium and vitamin D supplementation and preventive therapy as needed. Of note, vitamin D deficiency was recently linked to increased risk and severity of RA [51]. Screening and management of osteoporosis in RA patients have improved, although progress is still needed [52–54].

**Infection**

RA is associated with increased infection risk, which may be attributed to either impaired immune function associated with the disease itself or an effect of immunosuppressive therapy. In the
population-based Rochester Epidemiology Project, objectively confirmed infections and infections requiring hospitalization were more common among RA patients compared to those without RA; the adjusted hazard ratios were 1.70 (95% CI, 1.42–2.03) and 1.83 (95% CI, 1.52–2.21), respectively [66]. Infection risk associated with RA was most evident in bone, joints, skin, soft tissues, and the respiratory tract. In this study, increasing age, the presence of extra-articular RA manifestations, leukopenia, comorbidities, and the use of glucocorticoids were predictive of infection risk [67]. RA was also independently associated with an increased risk of pneumonia in a large population-based case–control study involving >17,000 incident cases; the odds ratio was 1.84 (95% CI, 1.62–2.10) after adjusting for other pneumonia risk factors [68]. Serious infection was reported at a rate of 46.4 events per 1000 patient-years in a retrospective cohort of RA patients aged ≥66 years, which was higher than the rate seen in younger RA cohorts [69]. Factors predictive of infection risk in the elderly included higher comorbidity, rural residence, greater disease severity, and history of previous infection, with the risk further increased by glucocorticoid use and to a lesser extent by the use of TNF inhibitors and DMARDs.

In a retrospective cohort of 27,710 RA patients, the use of DMARDs (without glucocorticoids) did not influence the risk of serious infection, whereas the use of glucocorticoids was associated with an increased serious infection risk (adjusted rate ratio for glucocorticoids vs no use of DMARDs or glucocorticoids: 1.9 [95% CI, 1.75–2.05]) [70]. Subsequent findings from a healthcare database analysis supported the increased risk associated with glucocorticoid therapy: among RA patients aged ≥65 years, treatment with prednisolone 5 mg/day or equivalent for 3 years was associated with a 2-fold risk of current serious infection vs non-use (adjusted odds ratio 2.00 [95% CI, 1.69–2.26]) [71]. Meta-analyses of controlled clinical trials indicate that TNF inhibitors show a non-significant tendency to raise serious infection risk [72–74]. In the prospective CORRONA registry involving 7971 RA patients, the adjusted rate of infection was higher with methotrexate compared with other conventional DMARDs and was further increased by the use of TNF inhibitors either alone or in combination with methotrexate [75]. TNF inhibitors used alone or in combination with methotrexate also increased opportunistic infections. In the British Society for Rheumatology Biologics Register (BSRBR), TNF inhibitors were associated with an increased risk of serious infection compared with conventional DMARDs, particularly during the first 6 months of therapy [76]. Finally, recent data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry suggests that the risk of serious infection with TNF inhibitors varies by agent, with etanercept having a lower risk than the anti-TNF monoclonal antibodies adalimumab and infliximab [77].

**Malignancy**

RA may confer an increased risk of certain malignancies but may protect against others. In a meta-analysis, RA was associated with a 2-fold increase in the risk of lymphoma compared with the general population (standardized incidence ratio [SIR] = 2.08; 95% CI, 1.80–2.39), with higher risk for Hodgkin lymphoma (SIR = 3.29) than for non-Hodgkin lymphoma (SIR = 1.95) [78]. RA was also associated with a 63% increased risk of lung cancer compared with the general population but with a 23% decreased risk of colorectal cancer and a 16% decreased risk of breast cancer. TNF inhibitors, whether used alone or with methotrexate, were not associated with lymphoma risk in large observational registries [79,80], although some association between TNF inhibitors and lymphoma risk has been reported in small cohorts [81,82].

Several reports suggest that TNF inhibitors increase the risk of melanoma and non-melanoma skin cancer [83–85]. For example, in the National Data Bank of Rheumatic Diseases, the use of infliximab or etanercept increased the odds of melanoma by approximately 2.5-fold, and infliximab also increased the odds of non-melanoma skin cancer by 1.7-fold [85]. A recent report from the BSRBR registry showed that TNF inhibitors (SIR = 1.72) and conventional DMARDs (SIR = 1.83) increased the risk of basal cell carcinoma and squamous cell carcinoma in RA compared with the general population [86]. Taken together, these findings suggest that treated RA patients should use sun protection and be monitored for skin cancer.

Pooled analyses of clinical trials found that rituximab, abatacept, and tocilizumab were not associated with malignancy risk [87–89], but further evaluation in real-world clinical practice is still needed.

**Psychosocial aspects**

**Health-Related Quality of Life (HRQOL)**

HRQOL is significantly impaired in RA owing to pain, fatigue, and functional deficits [90]. Moreover, the decrements in HRQOL are associated with reduced productivity, work loss, and work disability. The Short Form-36 (SF-36) is the tool most often used to assess HRQOL in RA. It consists of 36 questions across 8 domains, including limitations in physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The domains are summarized to yield physical component summary (PCS) and mental component summary (MCS) scores, which range from 0 (worst) to 100 (best) and which are compared to age- and sex-matched norms having a mean of 50.

The impact of RA on HRQOL is evident from a study of SF-36 data collected from patients with RA and healthy controls [Fig. 2] [91]. The findings are consistent with SF-36 data collected at baseline in large randomized, controlled trials of various biologics, in which the greatest impairments were seen in the physical function, role physical, bodily pain, and vitality domains and thus were reflected more in the PCS than in the MCS measure. In the Etanercept in Early RA (ERA), Combination of Methotrexate and Etanercept in Active Early RA (COMET), and PREMIER trials, where patients had RA for a mean duration <1 year, the baseline PCS scores were 28–32 and the baseline MCS scores were 42–47 [92,93]. In general, similar decrements were seen in trials of patients with established RA [94–96].

The effect of treatment is greatest in magnitude on the domains having the lowest scores at baseline, and consequently improvements in PCS are greater than those in MCS [90]. In early-stage disease, the improvement in HRQOL with methotrexate is similar in magnitude to the improvement with TNF inhibitors [92]. In patients on background methotrexate therapy, the addition of a TNF inhibitor or another biologic produces significantly greater HRQOL improvement compared with adding placebo [93–97]. Nevertheless, the PCS, MCS, and domain scores remain below the normative mean of 50, indicating that HRQOL is still impaired [89], but further evaluation in real-world clinical practice is still needed.

**Fatigue**

Fatigue is a subjective feeling of debilitating tiredness or weakness that interferes with physical and social activities. In RA, fatigue differs from normal tiredness in that it is extreme, often unrelated to prior activities, and unresolving [99]. Fatigue is significantly more pronounced in RA patients compared with healthy controls [100,101]. In a study comparing 122 RA patients with the same number of matched controls, greater fatigue was associated with...
In a 1-year longitudinal study, the proportions showing increased vs decreased fatigue severity were generally comparable (54% and 45%, respectively) [102]. Surprisingly, baseline increased vs decreased fatigue severity were generally comparable [101]. In a 1-year longitudinal study, the proportions showing more anxiety, disability, and social stress, and less social support [101]. Findings have been negative, however, and swollen and tender joint count, pain, and patient function were shown to be more important correlates of fatigue in the RA population.

Several instruments have been used to assess fatigue in RA and other conditions, including the Profile of Fatigue (ProF) and the Multidimensional Fatigue Inventory (MFI) [105]. In clinical studies, fatigue is more often assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, which has been validated for use in RA [106]. FACIT-Fatigue is strongly associated with the vitality domain on the SF-36 and has the ability to distinguish patients according to ACR response levels. FACIT-Fatigue is also correlated with Health Assessment Questionnaire (HAQ) and patient global and pain visual analog scores [107]. FACIT-Fatigue consists of 13 questions scored on a 0-4 Likert scale; total scores range from 0 to 52, with higher scores indicating more fatigue.

The impact of biologics on fatigue has been evaluated in clinical studies. In the adalimumab trials, the improvement in FACIT-Fatigue ranged from −3 to −7 points across trials, with a change of −4 points considered to represent a minimum clinically important difference [108]. However, a meta-analysis of 10 randomized trials concluded that the effect of biologics on fatigue was small; the effect size was 0.45 (95% CI, 0.31–0.58) for biologics overall and 0.36 (95% CI, 0.21–0.51) for TNF inhibitors [109]. The mechanism of fatigue in RA remains to be determined [110]. It does not correlate with erythrocyte sedimentation rate or joint counts, suggesting that it is not simply a manifestation of inflammatory joint disease. Elevated circulating cytokine levels may contribute to fatigue, inasmuch as TNF inhibitors and other biologics produce some improvement in fatigue. However, other factors including comorbid depression and anxiety, and lack of social support, may also be important contributors to fatigue [111,112].

**Depression**

Depression is common in RA and is estimated to occur in 13–20% of patients [113]. For example, in the baseline assessment of comorbid in the BSRBR registry, 19% of patients had previously received a formal diagnosis of depression [114]. When mild depressive symptoms are included, the prevalence may be as high as 40% [115]. Depression has not been consistently correlated with disease activity or progression in RA [107,109]. However, depression has an adverse impact on outcomes; it has been found to be associated with increases in mortality [116], cardiovascular morbidity [117] including myocardial infarction [118], and disability [119]. Moreover, depression is associated with reduced HRQOL. In a cohort of 307 RA patients who were followed up for 2 years, depressive symptoms were more important than radiographic damage or disease activity as predictors of decrements in the MCS of the SF-36 [120].

The etiology of depression in RA is not clear. However, patients are characterized as having a high prevalence of major life events preceding the onset of RA and the presence of personality disorders [121]. In addition, the multiple levels of stress response system activation in RA may ultimately influence disease-related outcomes such as depression [122]. Depressive symptoms have been associated with systemic inflammation, measured by hs-CRP levels, in multiple RA cohorts [123–125]. For example, in a cohort of 218 RA patients, depression scores measured using the Beck Depression Inventory II were positively correlated with CRP levels ($r = 0.46$; $P < 0.001$), and both were significantly correlated with pain [125]. Proinflammatory cytokines have been postulated to play a role in depression by altering the hypothalamic–pituitary–adrenal axis, but this remains an unproven hypothesis [126,127]. Among cytokines, IL-6 has been the most consistently elevated in depression, but little evidence is available to link this cytokine with depression in RA [128].

**Cognitive dysfunction**

Cognitive impairment was reported in 30% of RA patients in a cross-sectional study, with RA patients having significantly poorer scores for verbal fluency, logic memory, and short memory compared with healthy controls [129]. In this study, cognitive impairment was unrelated to RA clinical or treatment features or to disability. In another longitudinal cohort study, RA patients were classified as cognitively impaired if they performed 1 standard deviation below age–based population norms on at least 4 of 16 indices derived from 12 standardized neuropsychological measures [130]. Overall, 31% of the patients met this definition of cognitive impairment. After gender, race, disease duration and severity, hs-CRP level, and depression were controlled for, 4 factors independently predicted increased cognitive impairment: low education, low income, use of oral glucocorticoids, and the presence of cardiovascular risk factors. The same investigators also showed that the objective assessment based on the 12 standardized neuropsychological measures was not significantly
correlated with the cognitive impairment perceived by patients, although patient-perceived cognitive impairment was significantly associated with both depression and fatigue. Cognitive impairment was also associated with depression and pain, and with biocorrelates of inflammation and demyelination in other RA cohorts.

Interestingly, a long-term population-based study found that RA in midlife was associated with a 2.77-fold higher risk of cognitive impairment measured 2 decades later. Moreover, RA increased the risk for subsequent development of Alzheimer’s disease by 2.5-fold. In a small cohort of elderly RA patients, TNF inhibitors significantly improved Mini-Mental State Examination scores from a mean of 24.5 at baseline to 26.3 after 6 months. However, further work is needed to determine how treatment influences cognitive dysfunction in the general RA population.

Work performance and disability

RA causes work limitations across all domains of the Work Limitations Questionnaire, corresponding to a 5% decrease in work productivity. However, RA patients tend to select jobs that they can perform within their limitations; consequently, measures of work limitation are not affected to the same extent by RA as are HAQ and HRQOL measures. Besides the limitation in productivity, RA causes an estimated 30–40% of patients to stop working. HAQ is the major predictor of work disability, with patients who have manual jobs most likely to discontinue working.

Work disability has been related to treatment response, with the highest rates for nonresponders, intermediate rates for ACR 20% improvement criteria (ACR20) or ACR 50% improvement criteria (ACR50) responders, and the lowest rates for those achieving remission with DMARD therapy. Similarly, work productivity has been improved in clinical studies of TNF inhibitors, often in association with improvements in PCS on the SF-36. Nevertheless, work disability remains a major problem in RA, even in early-stage disease.

In the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database, which included information on 8039 patients from 32 countries, 37% of RA patients who were working at the time of diagnosis reported work disability at some point because of the disease. For patients diagnosed in the 2000s, the probability of continuing to work was 80% at 2 years and 68% at 5 years, with similar patterns in countries with high and low gross domestic product (GDP). In general, patients who continued to work had better clinical status measures and self-report scores compared to those who stopped working. Interestingly, the use of biologics was more common among those who stopped working compared with those who continued working (39% vs 32% in high gross domestic product [GDP] countries and 13% vs 8% in low GDP countries). These values could reflect selection bias in that patients with more severe disease, and hence greater work disability, may have been more likely to receive biologic therapy.

**Discussion**

The RA disease burden extends beyond the joint to include other tissues and organs, involving multiple comorbidities and psychosocial manifestations. With the introduction of DMARDs and biologics, considerable progress has been made in addressing the burden associated with joint damage, and now the focus needs to shift to reducing other aspects of the disease burden. Toward this objective, promising strategies include personalized medicine, which focuses on managing risk factors and identifying predictive biomarkers, and research on emerging treatments that target recently identified mechanisms in the complex pathophysiology of RA and its related systemic expressions.

Personalized medicine recognizes that the disease course and burden differ across individual patients. Risk factors need to be considered to identify which RA patients are at increased risk of specific disease manifestations, and similarly, predictive biomarkers are needed to identify which treatments are optimal for a given patient. Risk factors for many RA comorbidities are well recognized. For example, hypertension, dyslipidemia, insulin resistance, diabetes, obesity, lack of exercise, and cigarette smoking are well-known cardiovascular risk factors. Therefore, aggressive risk factor management may be necessary in each RA patient in order to reduce comorbid cardiovascular risk, consistent with the approach taken in patients with established cardiovascular disease.

With multiple therapeutic options available, predictive biomarkers are needed to help guide treatment decisions for individual patients. Additionally, earlier diagnosis would enable healthcare providers to initiate therapeutic interventions more quickly, when treatment is most likely to prevent progressive joint damage and reduce the systemic inflammation that contributes to various extra-articular and psychosocial manifestations.

The introduction of DMARDs enabled an approach to treatment based on the control of inflammatory reactions and immune cell activation mechanisms in the complex pathophysiology of RA, even in early-stage disease.
proliferation, and these therapies provide the basis for RA treatment today. Glucocorticoids and methotrexate have now been available for 60 and 40 years, respectively, and are used as initial therapy and in combination with biologics to guarantee optimal responses based on a treatment-to-target approach [4]. Leflunomide, the last DMARD developed, did not differ significantly from methotrexate in efficacy and safety in clinical trials; it now serves as a "rescue agent" for RA patients who cannot use methotrexate [146].

Currently available biologic therapies target monocye-derived cytokines (i.e., TNF, IL-6, IL-1p), the B-cell marker CD20, or the co-stimulatory cell surface molecule CD86 found on antigen-presenting cells. In clinical practice, use of these agents mainly affects the inflammatory joint process and, to a lesser extent, other systemic and extra-articular RA complications. The comorbidities and psychosocial aspects of RA may thus reflect, at least in part, systemic manifestations of inflammation and immune response that are not fully addressed by currently available therapies. It is tempting to speculate that new treatments blocking other cytokines may not only affect inflammatory joint processes but also other aspects of systemic inflammation. The proinflammatory cytokine IL-17A, for example, has been associated with impaired microvascular function and arteriolar compliance in RA patients, raising the possibility that it may contribute to cardiovascular comorbidities [147]. IL-17A inhibition has shown promising activity in early clinical trials that evaluated extra-articular manifestations of RA such as fatigue and HRQOL [148,149].

Targeting cytokine signaling by inhibiting specific Janus kinases is another new approach for downregulating immuno-inflammatory reactions in RA. The binding of many, but not all, cytokines to their respective receptors phosphorylates specific members of the Janus kinase family, which in turn mediate signaling processes that regulate the transcription of specific cytokine-controlled genes [150] and expand the inflammatory reaction.

**Competing interests**

Dr. Cutolo has received research grants from Bristol-Myers Squibb, Actelion, and Sanofi. Dr. Kitas has served as a consultant UCB and Astra-Zeneca, received honoraria from Abbott, UCB, and Pfizer, and received research grants from Pfizer. Dr. van Riel has received grants from and consulted for Bristol-Myers Squibb, Pfi zer, and received research grants from Pfi zer. Dr. Cutolo has received research grants from Bristol-Myers Squibb, UCB, Roche, and MSD. Dr. van Riel has received grants from and consulted for Bristol-Myers Squibb, UCB, Roche, and MSD. Dr. Cutolo has received research grants from Bristol-Myers Squibb, UCB, Roche, and MSD. Dr. van Riel has received grants from and consulted for Bristol-Myers Squibb, UCB, Roche, and MSD.

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