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The challenging interplay between rheumatoid arthritis, ageing and comorbidities

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Abstract

Background: The incidence of rheumatoid arthritis (RA) is expected to increase over the next 10 years in the European Union because of the increasing proportion of elderly people. As both RA and ageing are associated with emerging comorbidities such as cardiovascular disease, malignancies and osteoporosis, these factors will have a profound effect on the management of RA. In addition, both increasing age and comorbidities may independently alter commonly used RA-specific outcome measures.

Discussion: Age-related decline in immune cell functions (immunosenescence), such as a decrease in T-cell function, may contribute to the development of RA, as well as comorbidity. The chronic immune stimulation that occurs in RA may also lead to premature ageing and comorbidity. The interplay between RA, ageing and (emerging) comorbidities is interesting but complex. Cardiovascular disease, lung disease, malignancies, bone and muscle wasting and neuropsychiatric disease all occur more frequently in RA patients as compared to the general population. It is unclear how RA should be managed in 'today's world of multiple comorbidities'. Evidence that treatment of RA improves comorbidities is currently lacking, although some promising indirect observations are available. On the other hand, there is limited evidence that medication regularly prescribed for comorbidities, such as statins, might improve RA disease activity. Both ageing and comorbidity have an independent effect on commonly used outcome measures in the RA field, such as the Health Assessment Questionnaire (HAQ) and the clinical disease activity index (CDAI). Prospective studies, that also account for the presence of comorbidity in (elderly) RA patients are therefore urgently needed. To address gaps in knowledge, future research should focus on the complex interdependencies between RA, ageing and comorbidity. In addition, these findings should be integrated into daily clinical practice by developing and testing integrated and coordinated health care services. Adaptation of management recommendations is likely required.

Summary: The elderly RA patient who also deals with (emerging) comorbidities presents a unique challenge to treating clinicians. A paradigm shift from disease-centered to goal-oriented approach is needed to develop adequate health care services for these patients.

Keywords: Rheumatoid arthritis, Ageing, Elderly, Comorbidity, Multimorbidity

Background

By 2030, about one in four inhabitants of the European Union will be above the age of 65 [1]. The relevance of ageing is becoming more and more apparent in industrialized countries as, in parallel to an increase in life expectancy, birth rates are decreasing [1]. In an ageing population, it is expected that the number of patients with inflammatory arthritis, including rheumatoid arthritis (RA), will grow proportionally. RA is known to have a high disease burden and is associated with a substantial economic burden on patients, their families, and society [2, 3]. It is estimated that in England the annual direct healthcare costs of RA are approximately €780 million per year and the indirect costs related to work disability up to €6.75 billion per year [4]. A considerable proportion of these costs is due to the fact that RA is a complex disease associated with an increased prevalence of several comorbidities [5, 6]. These comorbidities can

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precede or accompany RA, and can be caused by the therapeutic armamentarium used in patients with RA. Substantial evidence indicates that the continuous systemic inflammation and immune dysfunction characteristic for RA plays a critical role in the development and acceleration of comorbidities [7]. Comorbidities most frequently seen in patients with RA include cardiovascular disease, lung disease, malignancies, osteoporosis, changes in body composition and neuropsychiatric disease. Most of these comorbidities occur more frequently than expected in RA patients as compared to the general population. As the number of comorbidities increase with age, and as patients with RA survive longer, more patients with RA will have comorbidities. Currently, the average patient with RA has two or more comorbid disorders [6, 8, 9].

Resolving the interplay between RA, comorbidities and its determinants is challenging. While the occurrence of (emerging) comorbidities is more common in RA, the clinical consequences of comorbidity are also more severe in these patients as compared to controls. Despite this observation, comorbidity is often underrecognized and undertreated [6, 10, 11]. Many guidelines and outcome measures for RA focus on RA as a single disease and disregard that presence of comorbidity is nowadays the rule and not the exception.

Future research is therefore urgently needed. However, to facilitate the identification of knowledge gaps, it is important to reflect on what is currently known. This narrative overview will first address the process of ageing and immuno-senescence in patients with RA. Next, existing data on the role of RA or its management on the occurrence or course of comorbidities is summarized. In the following part, literature on implications of ageing and comorbidities on outcome assessment and management of RA is presented. If available, results of meta-analyses or systematic reviews are presented. In the last part, it is shown how treatment for RA may positively influence comorbidity and how treatment of comorbidity may positively influence RA. We will show that research addressing this topic has been scattered across multiple disciplines and a solid evidence base upon which to build policy is currently lacking. To keep up with the continuing demographic shift of an ageing (RA) population, we need to expand our knowledge on ageing and emerging comorbidities in patients with RA in order to develop adequate health care services for these patients (Fig. 1).

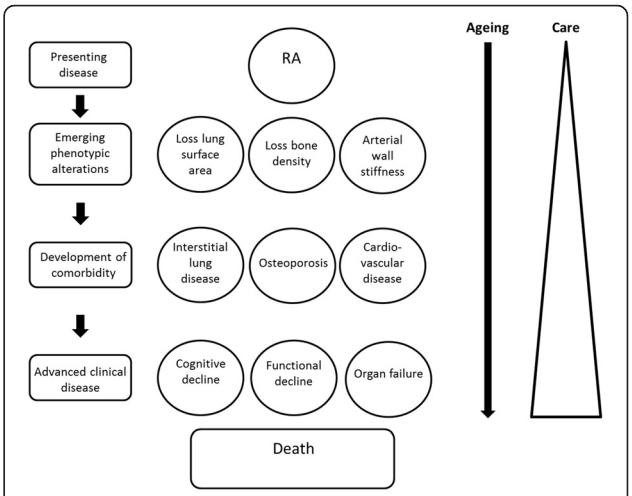

Fig. 1 Conceptual model for the effects of ageing and development of comorbidity in patients with RA. Abbreviation: RA, rheumatoid arthritis

Discussion

Rheumatoid arthritis, ageing and immunosenescence

To understand how ageing may affect RA and vice versa, one should first understand the contribution of the underlying cellular mechanisms. Senescence is a normal biological process that occurs in all organisms and involves the age-related decline in cell functions. In the context of the ageing immune system, this phenomenon is known as immunosenescence [12]. The mechanisms behind this process are multidimensional, but key features include age-related changes in both the adaptive and innate immune system. Immunosenescence of the adaptive immune system is characterized by loss of regenerative capacity and defects in T and B cell production, maturation and function (Fig. 2) [12–15]. Most profoundly, the ability to activate T cells in a productive manner is decreased. Because of the absence of an adequate T cell activation, the differentiation and effector function of B cells is also hindered [15, 16].

In addition to loss of effectiveness of the adaptive immune system, immunosenescence is also characterized by an enhanced chance to develop autoimmune disorders, including RA [16, 17]. The co-occurrence of declining immunocompetence and increasing autoimmune susceptibility appears contradictory at first sight. There are however parallels. It is suggested that the lack of immune

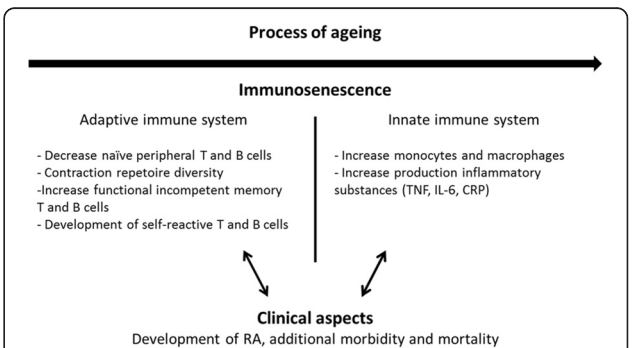

Fig. 2 The interplay between immunosenescence and development of rheumatoid arthritis [15–17]. Abbreviations: RA, rheumatoid arthritis; TNF, Tumor Necrosis Factor; IL-6, Interleukin-6; CRP, C-reactive protein

system stability predisposes to tolerance failure [12, 13]. For instance, CD28 deficiency in CD4 T-cells is associated with an increased production of proinflammatory cytokines [14]. In addition, alterations in the innate immune system cause monocyte and subsequent macrophage activation, resulting in an increase in levels of Tumor Necrosis Factor (TNF), Interleukin-6 (IL-6), C-reactive protein (CRP) and other inflammatory substances (Fig. 2) [12, 17]. This proinflammatory environment may, together with the development of self-reactive T and B cells, promote the development of RA. Alternatively, the continuous systemic inflammation in established RA may induce accelerated immunosenescence and development of other morbidities, such as cardiovascular disease (CVD) and cachexia (Fig. 2) [12, 17, 18].

Rheumatoid arthritis and presence of comorbidity

Cardiovascular disease

CVD usually encompasses coronary heart disease, peripheral vascular disease, cerebrovascular disease and congestive heart failure. It might also include prognostic markers of disease such as hypertension or dyslipidemia. The association of RA with accelerated atherosclerosis and eventually cardiovascular disease is a well-established one. The combined risk of cardiovascular morbidity is doubled in RA patients and there is a 60 % increase in risk of cardiovascular mortality [19–23]. In a meta-analysis of 14 observational studies including 41.490 RA patients by Avina-Zubieta et al., the risk of a myocardial infarction and cerebrovascular accident were increased by almost 70 % (pooled Relative Risk (RR) 1.7 (95 %-CI 1.4-2.0)) and 41 % (pooled RR 1.4 (95 %-CI 1.1-1.7)), respectively [20].

The RA-associated increased risk of cardiovascular morbidity and mortality can be explained by several processes that often occur simultaneously: (1) the effect of RA itself due to the presence of chronic systemic inflammation, (2) the effect that the presence of RA modulates important traditional cardiovascular risk factors or (3) the use of RA-specific medication such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease modifying anti-rheumatic drugs (DMARDs) [5]. Smoking, hypertension, insulin resistance, physical inactivity, dyslipidaemia and obesity are highly prevalent in people with RA as compared to the general population [24]. A recent meta-analysis suggested that the risk of cardiovascular events is increased when patients with RA frequently use corticosteroids ((RR) 1.5; 95 %-CI 1.3-1.6; $p < 0.001$) and NSAIDs (RR 1.2; 95 %-CI 1.0-1.4; $p = 0.04$) [25]. Interestingly, in a study by Lindhardsen et al., based on approximately 10 000 patients with RA, the risk of a myocardial infarction in patients with RA was similar to the risk of MI in patients without RA who were 10 years older [26].

Lung disease

Interstitial lung disease (ILD) and pleuritis are one of the most common extra-articular manifestations of RA [27]. In addition, lung disease may also be related to drug therapy used in RA or related to other comorbid disorders. ILD is the most important pulmonary manifestation of RA. Bongartz et al. found in a longitudinal study of 582 RA patients and 603 non-RA individuals, that the lifetime risk of developing ILD was 7.7 % for RA patients and 0.9 % for non-RA individuals (HR 9.0 (95 %-CI 4.0-19.9)) [28]. The association between Chronic Obstructive Pulmonary Disease (COPD), and RA is less well established [29]. In a meta-analysis of Ungprasert et al., that included 4 retrospective cohort studies (32.675 RA patients and 122.204 controls), the pooled RR of incident COPD in RA patients versus controls was 2.0 (95 %-CI 1.6-2.5) [29]. However, confounding might be responsible for the association between COPD and RA as smoking is also a well-established risk factor for RA [29].

Malignancies

In a meta-analysis including a total of 21 studies, RA was an independent risk factor for the development of lymphoma and was associated with a lymphoma risk that is approximately two-fold increased (standardized incidence ratio (SIR) 2.1, 95 %-CI 1.8-2.4) [30]. The risk on lymphoma appears to be especially higher in patients with high RA disease activity and presence of rheumatoid factor [31, 32]. There seemed to be a decreased risk for colorectal cancer (SIR 0.8, 95 %-CI 0.7-0.9) [30]. In a retrospective population cohort study among 84.475 RA patients who were observed for 405.540 person-years, it was found that RA patients had a significant higher risk of developing lung (SIR 1.7, 95 %-CI 1.5-1.8), liver (SIR 1.9, 95 %-CI 1.3-2.6), and oesophageal cancer (SIR 1.8, 95 %-CI 1.2-2.5), but a lower risk of prostate (SIR 0.7, 95 %-CI 0.6-0.7), breast (SIR 0.6, 95 %-CI 0.6-0.7) and ovarian cancer (SIR 0.6, 95 %-CI 0.5-0.8) cancer [33].

A recent systematic review of 49 studies showed that RA patients who used a TNF-inhibitor did not have an additional increased risk for malignancies in general, nor for lymphoma or non-melanoma skin cancer as compared to RA patients who did not use a TNF-inhibitor. However, the risk of melanoma might be increased (adjusted Hazard Ratio (HR) 1.5 (95 % CI 1.0-2.2)) [34].

Osteoporosis and changes in body composition

Another important group of RA associated comorbidities include bone and muscle wasting. Osteoporosis is characterized by a decline in bone mineral density (BMD), which may eventually increase the chance of developing fragility fractures [35]. The lifetime fracture risk of a patient with osteoporosis is as high as 40 % [35]. In

a study that included more than 30.000 RA patients selected from the British General Practice Research Database, the RR of a hip fracture was 2.0 (95 %-CI 1.8-2.3) and 2.4 (95 %-CI 2.0-2.8) for a vertebral fracture [36].

Cachexia due to systemic inflammation is characterized as the involuntary reduction in lean body mass (LBM) while fat mass tends to be maintained or even increased so that the body mass index (BMI) remains stable [37–40]. It has been shown that low LBM and higher fat mass is associated with a low BMD, even after controlling for potential confounders such as age, race, sex, height and grip strength [41, 42]. Specifically, He et al. showed among 17.891 individuals, that those with sarcopenia were two times more likely to have osteopenia or osteoporosis as compared to subjects without sarcopenia (OR 2.0; 95 %-CI = 1.6-2.6) [42]. The prevalence of cachexia in RA patients highly varies between patient populations and prevalence rates between 26-71 % have been reported [39]. The increase in fat mass is suggested to be a risk factor for the development of the metabolic syndrome and cardiovascular disease [40]. However, there are currently no studies that analysed cachexia in relation to cardiovascular mortality in RA.

Cognitive impairment, depression and anxiety

A few small-size studies have evaluated the impact of cognitive impairment in patients with RA [43–46]. These studies suggest that cognitive impairment is more frequently observed in patients with RA as compared to controls [43, 44]. In one long-term population-based study of Wallin et al., RA in midlife was associated with cognitive impairment two decades later, even when correcting for concomitant cardiovascular disease (OR (95 %-CI): 2.7 (1.2–6.1)) [47]. In another study that did not include a control group, an impairment in visual-spatial tasks was detected in 71 % of 30 included patients [44]. Cognitive impairment is also associated with more functional limitations, pain and depression in patients with RA [46, 48]. Potential risk factors for cognitive impairment are educational level, income, oral glucocorticoid use and presence of CVD risk factors [45].

Depression and anxiety are highly prevalent in patients with RA and are associated with poorer RA outcomes [49]. In the United States, the 12-months prevalence estimates of depression and anxiety disorders in the general population were 6.6 % and 18.1 %, respectively [50, 51]. Especially the prevalence of depression is considerably higher in RA patients. In a meta-analysis that included 13.189 patients with RA from 72 studies, the prevalence of a major depressive disorder was found to be 16.8 % (95 %-CI 10 %-24 %) [52]. The prevalence of anxiety disorders in patients with RA varied between studies from 13 % to 22 % [53, 54].

Effect of ageing and comorbidities on RA-specific outcome measures

The functional status of a patient with RA and response to treatment is measured by several disease-specific outcome measures, such as the Disease Activity Score –28 (DAS28), Health Assessment Questionnaire (HAQ) and the American College of Rheumatology (ACR) remission criteria [55–57]. These outcome measures are often used in randomised controlled trials (RCTs). The inclusion of patients in these RCTs is however restricted by stringent criteria. Therefore, patients included in RCTs often not resemble the spectrum of patients treated in the 'real world', i.e. elderly patients who often face comorbidity and polypharmacy.

Notwithstanding, several studies suggest that both ageing and comorbidity may independently alter commonly used RA-specific outcome measures, including joint scores, remission and response criteria and functional disability assessments [58–66]. In a population study of Krishnan et al. among 1530 adults in Finland, 76 % reported some pain and 83 % reported less than perfect general health. The overall mean value of the Visual Analogue Scale (VAS) pain was 20 mm [63]. Ageing was an independent predictor for higher scores on both the pain VAS and global assessment VAS in this study [63]. Sokka et al. concluded that only 15 % of the general population > 50 years old meet all four ACR remission criteria [64]. This finding suggests that the current remission criteria may not accurately identify remission in elderly patients. Ranganath et al. evaluated 1584 RA patients in a prospective cohort study and found that increasing numbers of comorbidities were independently correlated with less improvement in the clinical disease activity index (CDAI) after initiation of anti-rheumatic treatment [58]. The improvement in CDAI was 3.9 units greater in patients with three or fewer comorbidities as compared with patients with nine or more comorbidities [58]. In a study that included 380 RA patients by Radner et al., it was concluded that increasing levels of comorbidities are associated with increasing levels of disability within each domain of the HAQ [66].

Implications of ageing and comorbidity for treatment of RA

Rheumatologists' perspectives on elderly patients with RA and comorbidity

Nowadays, intensive anti-rheumatic treatment strategies that adhere to the treat-to-target principle are used to treat patients with RA [67]. Several studies have however described the phenomenon of 'age bias' when treating elderly patients with RA. Age bias may eventually result

in initiation of less intensive treatment regimens [68, 69]. In a study by Kremers et al., younger patients with RA were significantly more likely to receive DMARDs at an early stage (HR per 10-year decrease in age 1.4; 95 %-CI 1.3-1.5) as compared to their older counterparts [68]. Even when the level of disease activity and number of comorbidities were comparable between younger and older patients, rheumatologists still preferred the less intensive treatment option in older patients [68].

By using data from the CORRONA registry Tutunctu et al. found that the percentage of younger RA patients who were on DMARD combination therapy (40.5 %) or on TNF-inhibitors (33.1 %) was considerably higher than that of older RA patients (30.9 % and 25.0 %, respectively; $p < 0.001$) [70].

Modification of shared lifestyle risk factors

Smoking cessation, promoting physical activity and maintaining a healthy body weight are all pivotal steps to reduce both the prevalence and severity RA, several comorbidities (e.g. CVD) and to reduce overall mortality [71–73].

Cigarette smoking significantly increases the risk of developing RA [74, 75]. In a meta-analysis of observational studies, the OR to be diagnosed with RA in males with 20 or more pack-years of smoking was 2.3 (95 %-CI: 1.6-3.4) [74]. Although the exact mechanism behind this effect remains uncertain, the process of citrullination is considered to be an important factor for the development of RA in the anti-citrullinated protein antibody (ACPA)-positive patients [75]. Whether (cessation of) smoking influences the disease course in patients with RA remains controversial. There is no clear association between smoking and HAQ, DAS28, CRP or the erythrocyte sedimentation rate (ESR) [71, 76, 77]. In a meta-analysis that combined the radiographic data of six cohorts it was concluded that smoking was not an independent risk factor for radiological progression in RA, but that the effect was mediated via ACPA [78].

Regular exercise training in patients with RA is associated with improvement of and functional ability (e.g. aerobic fitness and muscle strength) without exacerbating disease activity [79–82].

Studies that address the association between body weight and disease activity show conflicting results and a high body mass index (BMI) has been correlated with both higher [83–85] and lower RA disease activity [86].

The European League Against Rheumatism (EULAR) has formulated recommendations about the need and timing of cardiovascular risk assessment in patients with RA [87]. In general, cardiovascular risk assessment should follow national guidelines (in general be performed annually) [6]. However, currently, no RA-specific management model is available for risk assessment and management of cardiovascular disease. According to the EULAR recommendations, cardiovascular risk prediction charts (e.g. Framingham Risk Score) should be multiplied by a factor of 1.5 in case two out of three of the following criteria are present: (1) disease duration > 10 years; (2) presence of rheumatoid factor or ACPA; (3) presence of extra-articular manifestations [87].

Unfortunately, up to our knowledge, there are at this moment no RCTs that assess the efficacy of antihypertensive agent or statins on cardiovascular endpoints exclusively in RA patients.

Does treatment of RA improve comorbidities?

The possible beneficial effects of anti-rheumatic treatment on concomitant cardiovascular disease has not been addressed in prospective RCTs. As mentioned before, patients with comorbidities are in fact often excluded from these RCTs. Most research concentrates on the question whether anti-rheumatic therapy may prevent the occurrence of cardiovascular events. Since both RA and atherosclerosis are inflammatory diseases, anti-rheumatic therapy may also inhibit various inflammatory pathways responsible for atherosclerosis. The exact mechanism is unknown, but beneficial effects on lipoprotein functions and on macrophage cholesterol metabolism have been described [88]. A recent meta-analysis of 28 observational studies suggests that the risk of cardiovascular events can be decreased by the use of TNF-inhibitors (RR 0.7; 95 %-CI 0.5-0.9; $p = 0.005$) and methotrexate (RR 0.7; 95 %-CI 0.6-0.9; $p = 0.007$) [25].

With regard to osteoporosis it has been suggested that TNF-inhibitors prevent further generalized bone loss by inhibiting bone resorption [89]. However, in most of these short-term and open-label trials, TNF-inhibitors were combined with methotrexate. Therefore, it needs to be determined whether this protective effect can be attributed to use of TNF-inhibitors by itself or the use of combination therapy and hence better RA disease control. In addition, no fracture data are currently available [89]. Interestingly, in early RA, short-term use of glucocorticoids may have a positive effect on BMD, due to its strong anti-inflammatory effects [90]. In a randomized, placebo-controlled, double-blind 2-year study by van der Goes et al., addition of 10 mg prednisone daily to a methotrexate-based tight control strategy did not result in a negative effect on BMD in early RA patients on bisphosphonates [90].

Few studies have prospectively examined the impact of anti-rheumatic treatment on body composition [91–95]. A small-sized randomised study of 21 months duration by Engvall et al. including 40 patients, the use of TNF-inhibitors was associated with an increase in body fat mass (+3.8 (1.6-5.9) kg in the TNF inhibitor group vs +0.4 (−1.5-2.2) kg ($p = 0.04$) in the conventional synthetic

DMARD group). There were no changes in muscle mass or lipid profile [92]. Other studies with a shorter follow-up duration failed to show a change in body composition [93–95]. It needs to be determined whether these possible changes in body composition can be confirmed in other studies and if so, whether they are associated with development of cardiovascular disease on the long term.

In a recent systematic review and meta-analysis, the effect of TNF-inhibitors on depression and anxiety were evaluated [96]. Overall, effects were small or not significant. However, many studies have shown that antirheumatic therapy improves important patient reported outcomes including general well-being, fatigue and quality of life [97].

Does treatment of comorbidities improve RA?

There is some evidence that medication regularly prescribed for comorbidities, such as statins, might also improve RA disease activity measures and lower inflammatory markers [98, 99]. In addition to their lipid-lowering effects, statins also exert an anti-inflammatory function, which is held responsible for the beneficial effect on RA disease activity. In the randomised, placebo-controlled Trial of Atorvastatin in Rheumatoid Arthritis (TARA), it was found that addition of atorvastatin to standard antirheumatic therapy significantly improved the DAS28 as compared to placebo (treatment group: −0.50, 95 %-CI −0.8 to −0.3; placebo group: +0.03, 95 %-CI −0.2 to 0.3) [99]. In a recent cohort study by Schoenfeld et al., it was concluded that statin use was independently associated with a 21 % lower risk of all-cause mortality among patients with RA (HR 0.8, 95 %-CI 0.7-0.9) [99].

There is limited evidence that denosumab, a human monoclonal antibody against the Receptor activator of nuclear factor kappa B ligand and used in the treatment of osteoporosis, may inhibit the development of joint erosions in patients with RA [100, 101]. However, denosumab had no effect on joint space narrowing or on RA disease activity [101].

Although selective serotonin reuptake inhibitors have been reported to exibit anti-inflammatory effects in addition to their antidepressant effects, there is currently insufficient evidence that treatment of depression positively or negatively influences RA disease-specific outcome measures and other clinical outcomes [102–104]. In addition, the evidence to routinely prescribe antidepressants as analgesics in patients with RA is also inconclusive [105].

Conclusions

The research to date has successfully identified the epidemiology of comorbidity in patients with RA, a variety of determinants that influence outcome and to some extent the consequences associated with the presence of comorbidity. However, the magnitude of effect of ageing and comorbidity on outcome measures and RA management is largely unknown. Moreover, for many of the comorbidities, it is equally unclear whether they should be managed similarly in middle aged versus older patients. It seems clear that elderly RA patients who also face comorbidity will need a different management approach since the needs of these patients are more than just the sum of needs in relation to single diseases [106]. The symptoms of RA and comorbidities may be overlapping, treatments may interact, underlying pathophysiology may be shared and the course of all diseases may be altered. As a consequence, the current RA treatment strategies might not be directly translatable to elderly patients with RA and comorbidity [107]. Research should focus on the impact of comorbidities on screening, diagnosis and outcome measurement of patients with RA. Nowadays, elderly patients with comorbidities are often excluded from intervention studies [108]. Future clinical trials should however take the complex treatment-reality of these patients into consideration by developing for instance comprehensive comorbidity measures in order to correct for confounding and effect modification in clinical trials [109, 110]. This may ultimately result in the development of recommendations that can guide the complex management decisions that need to be made in the case of an ageing RA patient who faces comorbidity. In doing so, a goal-oriented approach should be prioritized above a disease-centered approach. Maintaining maximal functional status and active social participation are essential components of a goal-oriented approach. Avoiding inefficient healthcare utilisation and medication side-effects (e.g. suffering more from the treatment than from the disease) is important [111].

We propose the following priority clinical research areas:

- Improve our understanding on the role of RA and its management on ageing and occurrence as well as course of comorbidity.
- Explore barriers within patients and healthcare providers with regard to (1) prioritization of health issues and (2) executing a realistic care plan when dealing with comorbidity;
- Adjusting general and RA-specific outcome measures that account for ageing and comorbidity;
- Develop, evaluate and implement models for integrated, coordinated and goal-oriented care.

Availability of data and materials

Data available from published papers as per references.

Abbreviations
ACPA: anti-citrullinated protein antibodies; ACR: American College of Rheumatology; BMD: Bone Mass Density; BMI: Body Mass Index; CDAI: Clinical Disease Activity Index; CI: Confidence Interval; CRP: C-reactive Protein; CVD: cardiovascular disease; DMARD: Disease Modifying Anti-Rheumatic Drug; ESR: Erythrocyte Sedimentation Rate; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; HR: Hazard Ratio; LBM: lean body mass; OR: Odds Ratio; RA: rheumatoid arthritis; RCT: Randomised Controlled Trial; RR: Relative Risk; SIR: Standardized Incidence Ratio; TNF: Tumor Necrosis Factor; VAS: Visual Analogue Scale.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MO was de principal author of the article. AB participated in the elaboration, content and drafting of the manuscript. Both authors read and approved the final manuscript.

Authors' information
MO and AB are currently developing an outpatient clinic for RA patients with complex comorbidity. Their main research focus is on clinical-epidemiological research, specifically 'outcome' and 'societal and economic impact' of inflammatory rheumatic diseases.

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