MANAGEMENT OF RHEUMATOID ARTHRITIS IN ELDERLY PATIENTS

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Abstract
Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by polyarthritis, progresses with joint damage, and may involve extra-articular tissue. Although RA can develop at any age, its prevalence increases with age. The number of elderly RA patients is gradually increasing due to both the increase in the frequency of late-onset (age 65 and over) RA (LORA) patients and the increased life expectancy. RA is characterized by inappropriately accelerated immune aging that occurs in the early period and is independent of disease duration. Aging can affect both the onset and the clinical phenotype of RA. Moreover, one of the most challenging issues for specialists is the treatment of RA in elderly patients. Targeted treatment of RA in elderly patients is inadequate or not optimally administered due to patients’ pre-existing comorbidities, polypharmacy, physicians’ concerns about possible drug side effects, and the lack of specific treatment guidelines for elderly RA patients. Elderly RA patients have been rarely and sometimes not even included in randomized controlled trials due to both age and comorbidities. Nevertheless, evidence for the safety and efficacy of specific RA treatments in the elderly population is gradually increasing. In elderly patients with RA, disease activity, all the comorbidities of the patient, and possible side effects of the drugs should be taken into consideration when making treatment decisions, and the treatment target should be individualized. In this review, the epidemiology of elderly RA patients, their comorbidities, briefly immune aging in RA, and the medical treatment approach in elderly RA will be discussed in light of studies.

Keywords: rheumatoid arthritis; elderly; treatment.

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Key Messages for Research and Practice

- Late-onset RA (LORA) and all RA patients over the age of 60 constitute the elderly RA population.
- Comorbidities are high in elderly RA patients, and these are important factors affecting drug selection and side effects.
- Based on real-life data in elderly RA patients, steroids are prescribed more frequently than disease modifying anti-rheumatic drugs (DMARDs), and conventional synthetic (cs)DMARDs/biologic (b) DMARDs agents have similar efficacy and safety in elderly individuals with RA as in young-onset RA patients.
Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, and autoimmune disease that specifically involves the joints of the hands and feet and is a heterogeneous disease with varying clinical findings and pathogenetic mechanisms. Both genetic and non-genetic risk factors (such as smoking, microbiota, female sex) contribute to the development of RA [1].

The prevalence of RA varies depending on age, sex, and ethnic regions. The prevalence of RA for American and northern European populations is approximately 0.5% to 1% [2, 3]. The majority of patients with RA are elderly and approximately half of patients are over 65 at the time of diagnosis [4, 7]. In a study conducted in the USA, the prevalence of RA among people aged over 60 was reported as 2% [8]. The highest incidence is seen between the ages of 65 and 80 [2, 4]. Approximately 70% of patients with RA are female [9]. Lifetime risk of developing RA is 3.6% in women and 1.7% in men [10]. Overall, the population of the elderly with RA is increasing due to increased life expectancy and increased incidence of elderly-onset RA [11-13].

This paper aims to review the comorbidities in elderly RA patients, clinical features, immune aging in RA, and especially the medical treatment approach.

Search strategy

We searched the databases of Scopus, MEDLINE/PubMed and Web of science using the keywords “rheumatoid arthritis”, [AND] “elderly” or “older” or “late-onset” or /[AND] “treatment” for original articles or reviews which focusing on management to RA in the elderly patients. The keywords “rheumatoid arthritis “, [AND] “immunosenescence” or “aging” were used to analyze the aging process in RA. Articles written in English, original articles and reviews were assessed for analyzed. Non-English articles, outdated studies (before 2000), case reports and studies did not meet the purpose of our review were excluded.

Late-Onset Rheumatoid Arthritis and Elderly Rheumatoid Arthritis: Definition

There is no precise limit for the age of onset of late-onset RA (LORA). Some researchers define it as RA that starts after the age of 65, while some define it as RA that starts after the age of 60 [7, 14]. The elderly RA population consists of LORA patients and classical-onset RA patients aged over 60. In other words, regardless of the age of onset, every RA patient aged over 60 is considered an elderly RA patient. The elderly RA population is expanding due to both increased life expectancy and increased incidence of LORA [13].

Immune Aging and Immunosenesence in Rheumatoid Arthritis

Both innate and adaptive immune systems change with aging. In old age, innate immune mechanisms tend to be more active, whereas the function of the acquired immune system generally declines. One outcome of immune aging is a low-grade inflammation. This process can thus contribute to the development of chronic inflammatory and autoimmune diseases [11, 15].

During the progression of RA, a multitude of alterations take place within the immune system as a consequence of the aging process. T cells are the primary constituents of the adaptive immune system and are particularly susceptible to alterations or perturbations. The generation of novel T lymphocytes diminishes with advancing age. Consequently, the mature T cells located in the periphery undergo a process of proliferation that is significantly increased, leading to their eventual depletion and senescence. According to Serhala L et al, the phenomenon of immunological aging, referred to as accelerated immune aging, occurs in patients with RA regardless of the length of the disease [13]. Furthermore, immune aging in RA is influenced by various mechanisms. These mechanisms encompass insufficient telomerase activity, diminished thymic functionality, deficiencies in DNA repair mechanisms, impaired regeneration of T cells, and excessive cytokine production [11, 16].

Clinical Features of Late-Onset Rheumatoid Arthritis

There are clinical and laboratory differences between LORA and classic-onset RA. Although there are differences in the literature, it is known that LORA shows more acute onset, more systemic involvement, and more polymyalgia rheumatica-like clinical findings compared to young-onset RA. In addition, LORA may also be accompanied by constitutional symptoms. In LORA, female predominance is less common than in classical onset; large joints are more frequently involved; anti-cyclic citrullinated peptide antibody (anti-CCP) and rheumatoid factor (RF) positivity are less frequent. As expected, comorbidities are prevalent in LORA patients [7, 13].
The prevalence of comorbidities is high in the general elderly population. The most predominant comorbidities that increase with age are cardiovascular diseases, diabetes mellitus (DM), and malignancies. In RA, the most common comorbidities are cardiovascular diseases, pulmonary diseases, infections, osteoporosis, depression, and malignancies [11, 12]. A larger number of comorbidities has been associated with a higher mortality risk in RA patients [13]. Besides mortality, health-related quality of life (HRQoL) and economic burden can be greatly influenced by various comorbidities in RA patients. According to a study including 2925 RA patients (mean age: 60.4±0.2 years, prevalence of RA patients over 65 years: 40.4%) and 14,625 non-RA control patients, approximately 60.4% of RA patients and 37.2% of non-RA patients had ≥3 comorbidities. More than 90% of RA patients had at least one comorbidity. The most frequent comorbidities were cardiovascular diseases (79%) and respiratory diseases (34.4%). Having ≥5 comorbidities was associated with lower SF-12 physical and mental scores and increased medical expenses compared to RA without any comorbidities. This study showed that patients with RA had a larger number of comorbidities than those without RA of the same age and sex [17]. Apart from the above-mentioned comorbidities, infections are also an important cause of morbidity and mortality in RA. It has been shown that age is an independent risk factor for serious infections in RA patients [13, 18].

Treatment Approach in Elderly Rheumatoid Arthritis

The treatment of elderly patients is challenging due to age-related comorbidities, polypharmacy, decreased renal clearance, and pharmacokinetic changes. In elderly RA patients, the treatment is even more difficult due to the presence of more comorbidities and the lack of sufficient data in randomized controlled trials, in addition to the above-mentioned factors. Current guidelines for RA do not include specific sections or recommendations for elderly RA patients. There is also no specific guideline for elderly people with RA. Evidence on the efficacy and safety of treatments for elderly RA patients is mainly based on real-life data. In this section of the paper, the results of recent studies on the efficacy, side effects, and safety of steroids and disease-modifying antirheumatic drugs (DMARDs) in elderly RA patients will be summarized.

The age of the patient is an important factor in determining the treatment agent. The general opinion is that DMARDs and steroids less frequently to elderly patients. A study looked at how the age of disease onset affected treatment and found that people with LORA used a mix of conventional synthetic (cs), DMARDs, and biologic (b) DMARDs less often and were treated with corticosteroids more often than people with classical-onset RA, even though they had the same length of disease and level of disease activity [19]. There are other studies supporting these data. In a prospective cohort study conducted using a database of elderly RA patients between 2008 and 2020 in Canada, 354 LORA patients and 518 young-onset RA patients were followed up. The study found that LORA patients who were in remission were more likely to only get one csDMARD treatment, without biologics or JAK inhibitors [20]. In the CORPUS-RA cohort study conducted to compare prescription patterns in RA patients over the age of 75 and young RA patients, disease activity in the two age groups was similar at the time of inclusion in the study and one year later. In the CORPUS study, when all patients aged under and over 75 years were compared, steroid use and comorbidities were found to be higher in patients aged over 75 [21].

The Swedish multicenter BARFOT cohort research looked at how the condition changed with age and sex. In the 8-year follow-up of the 2837 patients enrolled in the prospective trial, they were classified as being under 40 years old, between 40 and 54 years old, between 55 and 69 years old, or 70 years old or older. In comparison to all other groups, men under the age of 40 had a substantially lower DAS28, whereas women aged 70 and up had the highest Sharp van der Heijde Score (SHS). The use of bDMARD treatment was more common in patients younger than 40 years old, while patients older than 70 years old were typically given corticosteroids more often than people with classical-onset RA, even though they had the same length of disease and level of disease activity [21].

Besides treatment efficacy, another concern for patients and physicians is the safety of drugs. Drug side effects such as hepatotoxicity, bone marrow suppression, and especially infections are the most important determinants for physicians in the choice of drugs. In elderly patients, the risk of drug side effects, including hepatotoxicity, is an important factor in drug choice due to decreased renal clearance and polypharmacy. In general, elderly RA patients are more likely to be treated with lower doses of methotrexate (MTX) compared to young patients [19]. MTX may cause cytopenia, even at low doses, in elderly patients.
The most important reasons for this are reduced renal clearance, misuse of drugs, and simultaneous use of multiple drugs. In this case, folinic acid is an important treatment agent [23].

In a retrospective observational study that included 300 elderly RA patients (mean age: 74.3±5.8 years), side effects that occurred during RA treatment were evaluated. In this group, where 54% of patients received MTX, 52.3% received steroids, and 23% received biologics, 103 patients (34.3%) experienced adverse events. The most common side effect was infection, at a rate of 46.6%. Multiple logistic analyses showed that significant infection-related factors were the advanced Steinbrocker stage and the presence of respiratory diseases. The presence of DM was also identified as an independent risk factor for pneumonia [24].

In a retrospective study in which the incidence of biologics-based serious infections requiring hospitalization among elderly RA patients (>65 years) was examined, the number of serious infection events did not differ significantly between the biologic and non-biologic groups over a 3-year observation period. When risk factors for serious infections were evaluated, it was found that there were no differences in terms of disease duration, age, and MTX use, whereas prednisolone dose (4.7 ± 3.2 vs. 1.3 ± 2.0 mg/day, P < 0.001) and prednisolone use were higher in the group that developed infections [25].

In another study in which the safety of biologic agents in elderly RA patients was evaluated, it was found that being over 65 years old and the presence of pulmonary complications were factors leading to the discontinuation of biologic drug use compared to RA patients aged under 65 years. However, it was emphasized that >75 years of age did not pose a greater risk than the age range of 65-75 [26].

Elderly RA patients were also evaluated for DMARD efficacy and safety according to the age of onset of RA. This is the first study in the literature in which the efficacy and safety of RA treatment were compared between the two groups: LORA patients (mean age: 72.8 ± 6.4 years) and elderly RA patients with onset before the age of 60 (mean age: 67.2 ± 5.9 years). The improvement in CDAI and treatment response trends after 54 weeks were comparable between the two groups, 1040 LORA and 710 non-LORA elderly patients with RA, and no significant difference was reported in reasons for treatment discontinuation, including infections and serious adverse events [22].

According to real-life data, although the efficacy of TNF inhibitors in patients with LORA is as effective as that in patients with classical-onset RA, functional indices are lower due to comorbidities [27]. Abatacept is effective in both age groups. Although there is insufficient data, rituximab is less effective compared to patients with early-onset RA [28, 29]. In a study in France, it was reported that although rituximab showed similar clinical efficacy in all age groups, patients aged over 75 years had a lower clinical response than patients aged 65-75 years [29]. In a study conducted with Japanese patients on tocilizumab, those using tocilizumab were found to have higher retention rates, and fewer discontinuations were observed due to drug inefficacy compared to those using anti-TNFs [30]. Although drug treatment strategies for RA are relatively well defined, the evidence on treatment in elderly patients is still insufficient. There are no guidelines in the literature that provide treatment recommendations for elderly RA patients or guidelines established by relevant associations. However, the LORIS (Late-onset Rheumatoid Arthritis Registry) study is currently carried out by the Japan College of Rheumatology (JCR) and the Japan Rheumatism Friendship Association to provide evidence to update the JCR clinical practice guidelines and is planned to be published in 2024 [31].

In light of these observational studies, steroids are used more frequently and csDMARDs and bDMARDs are used less frequently in elderly RA patients. In many studies, these drugs have been claimed to be effective and safe. However, steroid use, dosage, and pulmonary problems are still important risk factors for the development of infections.

Conclusions

In conclusion, as life expectancy increases and the world population ages, the number of elderly RA patients engaged in RA treatment will increase over time. Increased comorbidities, increased multiple drug use, and pharmacokinetic changes in elderly RA patients are the most important factors affecting the drug choice of physicians, drug efficacy, and side effects. Despite advances, it is suggested in the literature that RA is undertreated or inadequately managed in elderly individuals. Recent articles and evidence from trials have shown that csDMARDs and bDMARDs have similar efficacy and safety in elderly individuals with RA as in young-onset RA patients. Nevertheless, disease activity, any comorbidities, and possible drug side effects should be taken into consideration when using DMARDs and steroids in elderly RA patients, and the treatment should be individualized.
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CONFLICTS OF INTERESTS
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REFERENCES


