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Treatment patterns of rheumatoid arthritis across different age groups

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a higher incidence in older adults. We aimed to analyze the differences in the choice of RA treatment regimens across various age groups. A retrospective cohort study using data from the Ankara Bilkent City Hospital Registry was conducted, involving 3,475 RA patients categorized into three age groups: 18-49, 50-64, and over 65 years. Key variables examined included demographics, comorbidities, and utilization of various treatment modalities, including disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor-alpha inhibitors (TNFi), targeted synthetic DMARDs (tsDMARDs), and other biological treatments. Statistical analysis was done with Jamovi software. The study found significant differences in drug prescriptions among age groups. Older patients (>65 years) were less likely to be prescribed methotrexate and sulfasalazine but more likely to receive leflunomide and colchicine. A decline in the use of TNFi and tsDMARDs with age was noted, while other biologics were consistently used across all ages. Our findings underscore the impact of age on treatment choices in RA, revealing a tendency towards less aggressive treatment approaches in older patients. We emphasize the importance of re-evaluating current treatment protocols to better accommodate the health needs of the aging RA population and enhance their quality of life.

Keywords: Rheumatoid arthritis, tumor necrosis factor-alpha inhibitors, targeted synthetic disease-modifying antirheumatic drugs, biological treatment, age, geriatric

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, multisystemic inflammatory disease. Its etiology remains not fully understood, although significant progress has been made in understanding its pathophysiology. Key players in RA's pathogenesis and the maintenance of inflammation include Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-6. The detection of anti-citrullinated peptide antibodies aids in diagnosing RA and provides insights into the disease's progression [1]. According to the Global Burden of Disease 2010 Study, RA's worldwide prevalence is estimated at 0.24% [2]. Incidence and prevalence rates are about twice as high in women as in men. Women face a lifetime risk of 3.6% for developing RA, compared to 1.7% for men [3]. The average onset age of RA is 55 years [4], with the highest incidence occurring between 65 and 80 years [5]. Incidence increases with age; approximately 2.2% of individuals over 55 are estimated to have RA [6]. "Elderly-onset RA" is the term for cases that begin after age 60 [7], accounting for 10-33% of all RA cases [8].

The worldwide geriatric population has been rising due to both population growth and increased life expectancy. Consequently, the number of elderly patients with rheumatoid arthritis (RA) is gradually growing, encompassing both aging late-onset and younger RA patients. This demographic is characterized by comorbidities and a heightened susceptibility to drug side effects and toxicities [9]. The pharmacokinetics and pharmacodynamics

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of drugs change with age as a result of decreased body fat distribution, total body water, albumin concentration, cardiac output, decreased hepatic blood flow and glomerular filtration rate [10,11]. These changes may contribute to the increased occurrence of adverse events [12], explaining the rise in side effects and toxicity with age. Aging is also linked with a higher risk of morbidity and mortality from infections, a risk further compounded by RA and its treatments. Consequently, these factors create challenges in treating RA in older patients. The geriatric age group is a delicate population, grappling with comorbidities, high systemic drug use, a higher incidence of drug-related adverse events, and diminished immune defenses against infections [13]. The coexistence of RA with other chronic diseases necessitates a multidisciplinary, comprehensive approach to address the health needs. Certain medications can escalate cardiovascular risks. Polypharmacy is a significant issue affecting treatment options in elderly RA patients, with drug interactions and increased side effects, along with liver and kidney impairments, potentially hindering optimal RA treatment. Furthermore, there is an elevated risk of malignancies in this demographic due to the immune aging process, chronic inflammation, and impaired DNA repair mechanisms associated with RA [14]. This poses an additional challenge in managing treatment in older patients.

Early and, if necessary, intensive treatment of rheumatoid arthritis (RA) is crucial to achieve the lowest possible level of disease activity, ultimately clinical remission, thereby minimizing potential damage. The geriatric age group is particularly susceptible to joint erosions and extra-articular manifestations of RA. Consequently, managing RA in this demographic presents numerous challenges, necessitating swift decisions regarding optimal treatment options. Clinicians play a vital role in tailoring treatments to individual patients. Although there are no specific contraindications for the use of disease-modifying antirheumatic drugs (DMARDs) and biological therapies in elderly patients, the experiences of using these therapies in younger RA patients have been more pronounced. Considering the prevalence of RA in older patients, this data indicated that further optimization of treatment options and outcomes for the geriatric age group is essential. Personalized treatment approaches, taking into account disease activity, comorbidities, and safety considerations, should be developed for geriatric patients.

Older individuals are often under-represented in clinical trials, leading to limited evidence on treatment approaches for this age group. Consequently, due to the concerns mentioned earlier, clinicians may lean towards a less aggressive treatment approach in older patients. Studies indicate that while access to rheumatological assessment for patients with RA is not influenced by age, combination therapy initiation is, on average, delayed by two years in older patients. Additionally, research shows that conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs) are less frequently used in older patients, despite having similar disease duration, activity, and functional limitations as younger patients [15-17]. Another study identified older age as an independent factor predicting the non-initiation of DMARDs within the first 12 months of diagnosis [18].

In this study, we aimed to identify patterns and preferences in treatment choices across different age groups. This will provide insights into the clinical management of RA in various patient populations in Türkiye.

Material and Methods

The Ankara Bilkent City Hospital Registry, established in 2023, serves as a resource for the retrospective analysis and documentation of patients diagnosed with inflammatory rheumatological diseases. By June 2023, a longitudinal aspect has been incorporated, transforming the registry into a single-center, observational, longitudinal cohort. This web-based system, characterized by its duplication-disabled feature, meticulously records data about various inflammatory rheumatological diseases seen in our clinic.

The focus of the current study is on patients diagnosed with RA, as determined by clinical diagnosis of rheumatologists. Eligibility for inclusion in the study was restricted to individuals aged 18 and over. We analyzed retrospective cohort data from 3,475 RA patients who had complete and relevant records up until 2023.

Key variables examined in this study included demographics, comorbidities, and treatment regimens. Patients were categorized into three age groups: 18-49 years, 50-64 years, and over 65 years. Within these age groups, we assessed the use of treatment modalities (ever/never). The analysis focused on the use of disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor-alpha inhibitors (TNFi), including etanercept, adalimumab, golimumab, certolizumab pegol and infliximab, targeted synthetic DMARDs (tsDMARDs), including tofacitinib, baricitinib and upadacitinib, and other biological treatments including tocilizumab, rituximab and abatacept. The study was approved by the Ankara City Hospital Ethics Committee (date: 2023, number: E1-22-3978) and was performed according to the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were made with Jamovi (v2.3.22, Sydney, Australia) [19]. Visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) were used to determine whether the variables were normally distributed. Normally distributed continuous values were expressed as mean±standard deviation (SD) and categorical variables as number and percentage. Further pairwise comparisons were analyzed with post hoc Tukey test or Mann–Whitney U-tests using Bonferroni correction and setting the statistical significance at 1.67% type I error level (where appropriate). p1 represents hypothesis between the Age 18-49 and Age 50-64 groups; p2, between Age 18-49 and Age 65=< groups; and p3, between the Age 50-64 and Age 65=< groups.

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Results

The mean age of patients was 39.7 (7.7) years in group 1, 57.2 (4.2) years in group 2, and 71.4 (7.1) years in group 3. The gender distribution was comparable between groups (female 76.8%, 75.2%, and 73.3%, p=0.181). As expected, the presence of comorbidities increased with age (44.4%, %77.9% vs 92%, p<0.001).

Table 1 shows the comparative use of medications in the age-stratified groups (18-49 vs 50-64 vs over 65, until 2023). There are significant differences in the use of specific drugs between the age groups. Methorexate usage was significantly lower in patients over 65 years of age (71.4%, 74.5%, and 64.3%, respectively, p<0.001), as was the use of sulfasalazine (32.6%, 36.3%, and 29.5%, respectively, p=0.001). Conversely, the prescription of leflunomide (31.1%, 43.1%, and 47.5%, respectively p<0.001) and colchicine (7.3%, 10.4%, and 14.4%, respectively, p<0.001) was significantly higher in this older age group. Notably, the use of hydroxychloroquine was more common in patients aged 50-64 years (64%, 72.1%, and 64.6%, respectively, p<0.001).

Table 1. Drug choices in rheumatoid arthritis patients according to age

	Age 18-49 (N=957)	Age 50-64 (N=1410)	Age 65=< (N=1108)	Total (N=3475)	P
Age, mean (SD)	39.9 (7.7)	57.2 (4.2)	71.4 (7.1)	56.9 (13.6)	<0.001
Sex, female n(%)	735.0 (76.8%)	1060.0 (75.2%)	812.0 (73.3%)	2607.0 (75.0%)	0.181
Comorbidity, n(%)	425.0 (44.4%)	1098.0 (77.9%)	1019.0 (92.0%)	2542.0 (73.2%)	<0.001
Methotrexate, n (%)	683.0 (71.4%)	1051.0 (74.5%)	712.0 (64.3%)	2446.0 (70.4%)	<0.001
Leflunomid, n (%)	298.0 (31.1%)	608.0 (43.1%)	526.0 (47.5%)	1432.0 (41.2%)	<0.001
Sulfasalazine, n (%)	312.0 (32.6%)	512.0 (36.3%)	327.0 (29.5%)	1151.0 (33.1%)	0.001
Hydroxychloroquine, n (%)	613.0 (64.1%)	1017.0 (72.1%)	716.0 (64.6%)	2346.0 (67.5%)	<0.001
Colchicine, n (%)	69.0 (7.2%)	147.0 (10.4%)	160.0 (14.4%)	376.0 (10.8%)	<0.001
Corticosteroids, n(%)	290.0 (30.3%)	354.0 (25.1%)	250.0 (22.6%)	894.0 (25.7%)	<0.001
TNFi, n (%)	143.0 (14.9%)	117.0 (8.3%)	62.0 (5.6%)	322.0 (9.3%)	<0.001
tsDMARDs, n (%)	44.0 (4.6%)	75.0 (5.3%)	30.0 (2.7%)	149.0 (4.3%)	0.005
Other biologicals, n (%)	54.0 (5.6%)	99.0 (7.0%)	74.0 (6.7%)	227.0 (6.5%)	0.400

TNFi: tumor necrosis factor-alpha inhibitors, tsDMARDs: targeted synthetic DMARDs

Regarding the use of biologics, a statistically significant decrease with age was observed in the use of TNFi (14.9%, 8.3%, and 5.6%, respectively p<0.001) and tsDMARDs (4.6%, 5.3%, and 2.7%, respectively, p=0.005). However, the use of other biologics (5.6%, 7%, and 6.7%, respevtively, p=0.4) remained relatively consistent across age groups.

Furtherpairwise pairwise comparison revealed that methotrexate use (p1=0.087), salazopyrin use (p1=0.063), and tsDMARDS use (p1=0.431) are similar between group one and two. Salazopyrin use (p2=0.130) and hydroxychloroquine use (p2=0.789) are found to be similar between group one and three. Leflunomid use (p3=0.029) and steroid use (p3=0.138) was found similar between group two and there. TsDMARD use was near statistically significant according to bonferroni correction between group one and three (p2=0.021).

Discussion

In treating older patients with rheumatoid arthritis (RA), preferences for TNFi and tsDMARDs decreased compared to younger patients, while other biologic therapies were used at similar rates across age groups. Leflunomide emerged as the most preferred DMARD in older patients. Our study demonstrates that age significantly impacts the choice of RA treatment. The results, highlighting distinct treatment approaches in elderly RA patients compared to younger ones, suggest a need to re-evaluate current treatment protocols and clinical decision-making processes for the elderly.

The older population is underrepresented in RA clinical trials. Thus, data on the efficacy and toxicity of drugs in older people are limited. This makes clinicians more reluctant to treat the elderly. A multicentre survey study has shown that treatment decisions of rheumatologists' are influenced by the patient's age [20]. There are also real-world data showing that optimal treatment may not be achieved or may be delayed in older patients.

Doubts about drug efficacy or side effects might influence clinicians' preferences for biological agents. However, clinical trials specific to the elderly are insufficient to clarify this issue. Literature reviews concluded that anti-TNF agents are less effective and pose a higher serious infection risk in older patients. Conversely, other studies indicated similar tolerability and safety profiles of biologic agents in young and elderly RA patients [21]. Research by J.H. Koh et al. showed that 63% of elderly RA patients using biologic agents achieved low disease activity at one year, with adverse event incidence comparable to those using conventional DMARDs [22]. Studies on golimumab and etanercept reported similar efficacy in young and older patients [23,24], but trials of tocilizumab and rituximab found their efficacy negatively affected by age [25,26]. Abatacept had the highest survival among bDMARDs for clinical response and tolerability in a Japanese cohort. These data support that there

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are situations in which patient age should be considered in the control of disease activity and in the choice of treatment, as well as the fact that it should not be mistaken to restrict the choice of treatment only by age factor.

Our study revealed that TNFi and tsDMARDs were less preferred in patients aged >65, likely due to physicians' concerns about side effects and potential cardiovascular impacts of biological therapies, particularly tsDMARDs. A study using the CORRONA database looked at the treatment choices of patients with young-onset and late-onset RA and also showed that the use of biological agents was lower in EORA [15]. In the same study, the use of methotrexate was shown to be more common in EORA. Our findings, however, indicated a preference for leflunomide over methotrexate, possibly due to challenges in adapting to methotrexate use and dosage adjustments in cognitively fragile groups with reduced renal clearance. In our study, colchicine was another agent that was preferred more often in older patients than in younger patients. Increasing comorbidities with advancing age and associated crystalline arthropathy in RA patients seem to have increased the frequency of colchicine use. Although hydroxychloroquine is the least toxic of the conventional DMARDs, we observed that it is less preferred in older patients [27]. The relationship between cumulative dose and retinal toxicity limits the use of hydroxychloroquine. Similarly, the use of sulphasalazine has decreased with age. The gastrointestinal toxicity of sulphasalazine is the reason for the decreasing tolerance of the drug, especially in older patients [27]. The fact that close follow-up in terms of gastrointestinal side effects is more difficult in elderly patients may explain the lower preference for sulfasalazine in our study. Another important finding of our study was that TNFi and tsDMARDs therapies decreased with age, whereas other biological therapies were preferred at a similar rate across age groups. This result may be due to a preference for these drugs because of safety concerns, or it may be due to the aggregation of data from patients with longer disease duration who are resistant to other biological therapies. Since we know that drug survival of other biologicals is better.

Our study is the study with the highest number of patients evaluating treatment selection in the geriatric age group. Considering the effects of local factors on drug selection, the fact that this is the first study from Türkiye is another strength of this study.

Our study has some important limitations. The data in the study were collected retrospectively from patient records. Although the mentioned treatments cannot be prescribed outside the electronic patient record system, there is still a possibility of data loss. Another limitation is the reliance on data collected from a single center. This limits the generalizability of the results. The lack of data on disease activity, disease duration, autoantibody profiles, and whether the use of combination therapy means that cause and effect cannot be fully established in some conclusions, and such conclusions have been avoided.

Conclusion

In conclusion, our study highlights significant differences in RA treatment choices across age groups. The management complexities of older patients have prompted substantial changes in clinical practice. Except for leflunomide and other biologics, older RA patients receive less aggressive treatment than younger ones, contrary to current guidelines. Managing elderly RA patients is challenging; treatment should be individualized, assessing risks, and maintaining tight disease control. Effective treatments should not be withheld from older patients. Further clinical research is essential to develop effective treatment strategies, meeting the health needs of our aging population and enhancing the quality of life for elderly patients.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was approved by the Ankara City Hospital Ethics Committee (date: 2023, number: E1-22-3978) and was performed according to the principles of the Declaration of Helsinki

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