

Geriatrik Romatoid Artritli Hastaların Klinik Özellikleri ve Biyolojik Hastalık Modifiye Edici Antiromatizmal İlaçların Sonuçları

Clinical Characteristics of Patients With Geriatric Rheumatoid Arthritis and Outcomes of Biological Disease Modifying Antirheumatic Drugs

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Öz

Amaç: Yaşam beklentisi ve kalitesindeki artış, daha iyi tedavi ve geç başlangıçlı RA tanısında artış olması nedeni ile geriatrik romatoid artrit (RA) popülasyonunda artış oluşmuştur.İlaç etkileşimleri, maligniteler, enfeksiyonlar ve toksisiteler geriatrik yaş grubunda dikkat edilmesi gereken önemli konulardır. Biyolojik ajan tedavisi alan geriatrik RA hastaları hakkında sonuç ve bilgiler yeterli değildir. Bizim bu çalışmadaki amacımız, geriatrik RA hastalarının klinik özelliklerini, biyolojik ajanların etkinlik ve güvenliğini ve tedavi sonuçlarını değerlendirmektir.

Gereç ve yöntemler: Bu çalışma romatoloji kliniğinde tanımlayıcı gözlemsel bir çalışma olarak tasarlanmıştır. Geriatrik hastalar 65 yaş ve üstü olarak tanımlandı. Biyolojik tedavi öncesi ve tedavi sırasında hastaların yaş, cinsiyet, akut faz reaktanları, otoantikörler, hepatik/böbrek fonksiyon testleri, ekstraartiküler organ tutulumu, kullanılan ilaçlar, hastalık aktivitesi, yan etki profili, enfeksiyon ve maligniteler değerlendirildi. Veriler normallik dağılımına göre sayı, frekans, yüzde, ortalama±standart sapma veya median olarak verildi. İstatistiksel analiz olarak Wilcoxon ve Friedman testleri kullanıldı.

Bulgular: Çalışmaya yaş ortalaması 69.3±4.6 yıl olan 56 geriatrik RA hastası alındı. Hastaların %25'i biyolojik ajan kullanmaktaydı. Geriatrik RA hastalarında biyolojik ajan tedavisi ile birlikte hastalık aktivitesi düzeldi. RA hastalarında kreatinin, glomerüler filtrasyon hızı, alanin aminotransferaz ve aspartat aminotransferaz düzeylerinde biyolojik ajan tedavisinin 6. ayında ve son vizitte bazal değerlere göre anlamlı bir farklılık saptanmadı. Takiplerde malignite, otoimmünite, enjeksiyon bölgesi reaksiyonları, mortalite ve hematolojik olaylar saptanmadı.

Sonuç: Bu çalışma, RA'lı geriatrik hastalarda biyolojik ajanların etkili ve güvenli olduğunu göstermiştir. Yaşlanma ile fonksiyonlardaki değişiklikler, komorbid hastalıklar ve diğer ilaçların kullanımı nedeniyle tedavinin bireyselleştirilmesi gerekebilir.

Anahtar Kelimeler: Romatoid artrit, geriatri, biyolojik ajanlar, hastalık düzenleyici anti-romatizmal ilaçlar

Abstract

Objective: There is an increase in the population of geriatric rheumatoid arthritis (RA) due to the increase in life expectancy and quality, better treatment and increased diagnosis of late-onset RA.

Drug interactions, malignancies, infections and toxicities are important issues in geriatric age group. Outcomes and information about geriatric RA patients receiving biologic agent treatment is not sufficient. The aim of this study was to evaluate the clinical characteristics of geriatric RA patients, the efficacy and safety of biological agents and the results of treatment.

Material and Methods: This study was designed as descriptive observational study at the rheumatology clinic. Geriatric patients were defined as 65 years of age or older. Age, sex, acute-phase reactants, autoantibodies, hepatic/renal function tests, extraarticular organ involvement, the drug used, side effect profile, disease activity, infection, and malignancy during the biological treatment were evaluated. The data were described as a number, frequency, percentage, mean±standard deviation or median according to the distribution of normality. Wilcoxon test, Friedman test were used for statistical analyses.

Results: Fifty-six geriatric RA patients with the mean age of 69.3±4.6 years were enrolled. The twenty-five percent of patients were treated with biological agents. The disease activity improved with biological agent therapy in geriatric RA patients. No significant difference was found for creatine, glomerular filtration rate, alanine aminotransferase, and aspartate aminotransferase in RA patients on the 6th months, and last visit of biological therapy compared to baseline. No malignancy, autoimmunity, injection site reactions, mortality, and hematological events were detected on the follow-up.

Conclusions: This study showed that biological agents are effective and safe in geriatric patients with RA. The treatment may need to be individualized due to changes in functions with aging, *comorbid diseases, and the use of other drugs.*

Keywords: *Rheumatoid arthritis, geriatrics, biological agents, disease-modifying antirheumatic drugs*

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease characterized by destructive polyarthritis and organ involvement such as lung, heart, and rarely kidney (1). The risk of developing RA varies between 1.7% and 3.6% in adults (2). The female to male ratio reaches 2.1 after the 5th decade and male domination is observed after the 7th decade (3). The RA prevalence in a population of Izmir-Turkey was found to be 0.49% (4). Age and sex adjusted prevalence of the general population was reported as 0.36% in this study (4). In addition, the prevalence of RA over 60 years of age was reported as 2% in another study (5). The mean age of onset for RA has been reported to increase over the previous decade (3,5).

The disease affects especially the small joints such as the metacarpophalangeal, metatarsophalangeal, proximal interphalangeal joints, also elbow, ankle, knee, and shoulder (1).

Extraarticular involvement of RA is as follows: keratoconjunctivitis sicca, rheumatoid nodules, vasculitis, episcleritis, pleural/pericardial effusions, interstitial lung disease, neuropathy, and rarely glomerulonephritis, tubulointerstitial nephritis (6). Clinical findings of late-onset RA may differ from young-onset patients due to sex distribution, acute onset, constitutional and polymyalgia rheumatica-like symptoms, serological negativity, lower extremity, and large joint involvement (7,8).

Early treatment is important in RA and variously conventional and biological disease-modifying agents are used to treat the disease. Uncontrolled disease with ineffective treatment and strategies lead to joint destruction, disability of physical function, daily life activities, morbidity and mortality (1). Several adverse effects associated with biological disease-modifying agents have been reported in RA (9). In some studies, the risk of infections or adverse events was higher in elderly patients treated with biological agents than younger patients; some studies have reported that they have similar safety profile (10,11).

Biological functions decrease gradually and linearly with increasing age and age-related changes occur in the immune system. Infection, cancer and autoimmune diseases are more common in the elderly due to the age-related remodeling of the immune system (12). Therefore, it may be necessary to be more careful in terms of drug use and monitoring in geriatric RA patients (13). The clinicians should be cautious about drug interactions, malignancies, infections and toxicities in the geriatric age group. Also, the outcomes of geriatric RA patients receiving biological agents are limited due to excluded the patients from randomized controlled trials (14).

The aim of this study was to evaluate the clinical characteristics of geriatric RA patients, the efficacy and safety of biological agents and the results of treatment.

Materials and Methods

This was a single-center retrospective descriptive study, in which geriatric patients diagnosed with RA were enrolled. Geriatric patients were defined as 65 years of age or older. We excluded the patients with infections, malignancies, and age under 65 years from the study. The diagnosis of RA had been established on the basis of the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria (15). The study was approved by the ethical committee of our university (Protocol No: 2019/47).

Demographic, clinical features, and laboratory test results such as anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) were obtained from patients' records.

The family history of RA, extraarticular organ involvement,the drug used, side effect profile, disease activity, infection, and malignancy during the treatment were evaluated. The disease activity, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), renal function tests, and alanine-aspartate aminotransferaseswere evaluated before, on the 6th month and on the last visit of biological agents. The cut-off values were 18 IU/ml and 4.99 U/ml for RF and anti-CCP, respectively. Disease activity was measured by the Disease Activity Score-28 (DAS-28) (ESR) for RA patients.

The data were analyzed using the Statistical Package for Social Sciences version 17.0 (SPSS, Chicago, IL, USA). The data were described as a number, frequency, percentage, mean±standard deviation or median [interquartile range] according to the distribution of normality. Wilcoxon test, Friedman test were used to analyze repeated measures. The results were assessed at 95% confidence interval and p-value<0.05 was accepted as statistically significant.

Results

Fifty-six geriatric RA patients (25% male, 75%female) with the mean age of 69.3±4.6 yearswere evaluated. The mean disease duration was 10.6±8.1 years. There was a family history in 20 (35.7%) of geriatric RA patients.The secondary Sjögren syndrome was present in 24 (42.9%), lung involvement in 4 (7.1%), and osteoporosis in 19 (33.9%) of the patients.RF was positive in 66.1% of patients and the median RF titer was 123.9 [4.5-99.4]IU/mL. It was 73.2% and 80.5 [0.6-200] U/ml for anti-CCP, respectively.

Thirty-five (62.5%) of geriatric RA patients were treated with methotrexate,23 (41.1%) with leflunomide, 12 (21.4%) with sulfasalasine, and 36 (64.3%)with hydroxychloroquinecombined by leflunamid or methotrexate.The demographic, clinical, and laboratory characteristics of geriatric RA patients are shown in Table 1.

Table 1. The demographic, clinical and laboratory characteristics of geriatric patients with rheumatoid arthritis

	Rheumatoid Arthritis (n=56)
Age, yearsmean±SD	69.3±4.6
Gender, female n (%)	42 (75)
Disease Duration, yearsmean±SD	10.6±8.1
Family history of RA, n (%)	20 (35.7)
RF(IU/mL) median[IQR]	123.9 [4.5-99.4]
Anti-CCP(U/mL) median[IQR]	80.5 [0.6-200]
Co-Morbid Disease (%)	
Hypertension	16.1
Diabetes Mellitus	12.5
Coronary Artery Disease	3.6
Initial use of steroid, mg/daymean±SD	7.4±4.3
Medical Treatment (%)	
Methotrexate	62.5
Leflunomide	41.1
Hydroxychloroquine	64.3
Sulfasalasine	21.4
Use of biological agents, previously n (%)	3 (5.3)
Exposure time of Biological agents, monthsmean±SD	27.6±15.7
Lung involvement, n (%)	4 (7.1)
Secondary Sjogren Syndrome n (%)	24 (42.9)
Osteoporosis n (%)	19 (33.9)

SD: Standard deviation; IQR: interquartile range, RF: rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide

The twenty-five percent of patients were treated with biological agents. The agents include abatacept (35.7%), rituximab (14.3%), adalimumab (21.4%), golimumab (14.3%), etanercept (7.1%), and certolizumab (7.1%). The DAS-28 (ESR) score was decreased on the 6th months compared to baseline (5.4±0.4 vs 3.7±0.3, p=0.001). The thirteen of patients taking biological agents reached to moderate disease activity on the 6th months.There was no significant difference for creatine, glomerular filtration rate, alanine aminotransferase, and aspartate aminotransferase in RA patients on the 6th months of biological therapy compared to baseline. Before biological therapy, the mean level of AST and ALT were 16.5±4.0U/L and 18.1±6.5U/L, respectively. The levels of AST and ALT were 19.6±6.4 U/L and 17.2±6.9U/Lon the 6th months, and 20.0±6.7U/L and 17.5±8.6U/L on the last visit, respectively.Hemoglobin, lymphocyte levels were increased while *leucocyte*, neutrophil, and platelet levels were decreased with biological therapy. The results on the follow-up of biological treatment for geriatric RA patients are shown in Table 2.

Table 2.The results on the follow-up of biological treatment for geriatric rheumatoid arthritis

Parameters	Baseline mean±SD	On the 6th months mean±SD	At the last visit mean±SD
Hemoglobin (g/dL)	11.5±0.8	11.8±1.2	11.9±0.9
Leucocyte(10 ⁹ /L)	8055.0±1355.1	7553.5±2175.4	7371.4±1696.5
Neutrophils (10 ⁹ /L)	4957.8±906.0	4230.7±1500.3	4129.2±1303.1
Lymphocytes (10 ⁹ /L)	2449.2±1202.5	2565.7±564.4	2657.1±789.7
Platelets (10 ⁹ /L)	280642.8±76719.8	252357.1±66688.2	250500.0±59457.4
ALT (U/L)	18.1±6.5	17.2±6.9	17.5±8.6
AST(U/L)	16.5±4.0	19.6±6.4	20.0±6.7
Creatine (mg/dL)	0.7±0.1	0.7±0.1	0,8±0,2
GFR (ml/dk/1.73 m ²)	85.4±15.6	87.9±17.5	83.0±13.5
Uric Acid(mg/dL)	4.6±1.7	5.0±1.8	4.6±1.7
Glucose(mg/dL)	99.2±29.8	96.8±24.6	95.5±37.9

SD: Standard deviation, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GFR: Glomerular Filtration Rate

The biological agents were changed in 6 patients receiving infliximab, adalimumab, certolizumab, abatacept due to no achieve the treatment target and history for zona zoster in a patient receiving infliximab. In addition, no other infections, malignancy, autoimmunity, hematological events, injection site reactions, and mortality were observed in geriatric RA patients.

Discussion

A population of geriatric RA has been formed due to the increase in life expectancy and quality. Also, the higher prevalence of RA in the elderly may be related to the better treatment of patients or increases in the diagnosis of elderly onset RA (16). In our study, the female/male ratio was 3/1 in geriatric population.

Extra-articular manifestation such as secondary Sjögren syndrome is frequently seen in elderly patients with RA compared to younger RA patients (8,17). Patients with long-term disease may have pulmonary nodules, interstitial lung disease, pleural effusion, respiratory bronchiolitis, and bronchiectasis (6). Interstitial lung disease was reported in 18.7% of late-onset RA patients (17). In our study, the lung involvement was detected in 4 patients and secondary Sjögren syndrome in 24 patients.

Osteoporosis is common and well-known complications in RA patients with a high risk of fractures (18). The presence of RA, steroid use, disease duration, and older age are independent risk factors for osteoporosis (18). The mean steroid dose prior to biological agent treatment was 9.7 ± 2.5 mg/day and 33.9% of the patients had osteoporosis in our study. Development of atherosclerosis and cardiovascular disease have increased in RA patients with geriatric age group (6,19). The long-term use of high-dose steroid and systemic inflammation may accelerate the process of atherosclerosis (6,19). Therefore, it would be an appropriate approach to reduce the steroid dose or discontinue the drug according to the disease activity. Of the patients included in the study, 16.1% had hypertension, 12.5% had diabetes mellitus, and 3.6% had coronary artery disease.

The goal of treatment is to reach complete remission or low disease activity according to the treat-to-target strategies (20). Individual treatment and careful follow-up are more appropriate approach in older patients with RA (14). Also, medical therapy as well as exercise programs and, if necessary, surgical approaches should be considered in geriatric RA patients (21). Pharmacological treatment options for RA treatment have increased, especially with advances in biological agents. The use of conventional or biological Disease Modifying Anti-Rheumatic Drugs (DMARDs) have been reported to be lower in elderly RA patients than in young people (22,23). TNF- α inhibitors was reported less or equally effective to reduce disease activity in elderly patients compared to younger patients with RA (11). There is insufficient evidence for the efficacy of tocilizumab, abatacept, and rituximab in elderly patients with RA (8).

The thirteen of patients taking biological agents reached to moderate disease activity on the 6th months. And, there was a significant decrease in DAS-28 (ESR) score at 6th months and 27.6 ± 15.7 months follow-up after biological agents in patients included in our study.

The closely and careful and monitoring is required in elderly patients due to changes in physiological function, *comorbid conditions*, multiple drug use, compliance with treatment, drug misuse, pharmacokinetic and pharmacodynamic changes of drugs (8,14). Drug-related adverse events may occur in geriatric patients due to age-related changes in renal functions such as the decrease in renal blood flow and creatinine clearance (12). Therefore, initial creatinine levels should be carefully monitored in patients who planned to start DMARD. The glomerular function rate is more helpful compared to creatine levels in dosage adjustment due to reduced muscle mass in elderly RA patients (21). In our study, the mean GFR was 85.4 ± 15.6 at baseline and 87.9 ± 17.5 on the 6th months of biologic agents. There was no statistically significant difference for transaminase, creatine levels and GFR on the follow-up.

The biological DMARDs may lead to more infective complications in elderly patients due to comorbid diseases such as diabetes or age-related changes in immune defense mechanisms (14). Infusion reactions, fungal infections, tuberculosis/latent tuberculosis reactivation, malignancies, heart failure, hemocytopenia, liver, and kidney function impairment may occur with biological agents (9). On the contrary, some registries showed non-significant increases for severe infections with anti-TNF- α agents in patients over 65 years (24). In our study, there were no malignancy, autoimmunity, injection side reactions, infection except for herpes zoster, and mortality in geriatric RA patients.

In conclusion, disease activity have improved with biological agents in geriatric RA patients. The treatment may need to be individualized due to changes in functions with aging, *comorbid diseases*, and *another drugs*. *The present study has shown that biological agents were effective and safe in geriatric patients with RA.*

Conflict of Interest: All authors declare that no conflict of interest.

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