MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

ARAŞTIRMA MAKALESİ
RESEARCH ARTICLE
CBU-SBED, 2021, 9(2): 243-250

Yaşlı Başlangıçlı Romatoid Artrit, Genç Başlangıçlı Romatoid Artritten Farklı mı?

Is Elderly-Onset Rheumatoid Arthritis Different From Younger-Onset Rheumatoid Arthritis?

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Gönderim Tarihi / Received:08.12.2021
Kabul Tarihi / Accepted: 16.12.2021
DOI: 10.34087/cbusbed. 10.34087/cbusbed.10332757

Öz

Giriş ve Amaç: Yaşlı başlangıçlı romatoid artritli (YBRA) hastaları, genç başlangıçlı romatoid artritli (GBRA) hastalar ile sosyodemografik, klinik, radyolojik ve tedavi yanıtları açısından karşılaştırmaktır.

Gereç ve Yöntemler: 2010 American College of Rheumatology-Rheumatoid Arthritis (ACR-RA) sınıflama kriterlerini karşılayan 422 romatoid artrit (RA) hastası geriye dönük olarak değerlendirildi. Hastalık semptomlarının başlangıç yaşı ≥60 olan hastalar YBRA, <60 olanlar GBRA olarak kabul edildi. Sosyodemografik özellikler, komorbid hastalıklar, laboratuvar değerleri, eklem tutulum paternleri, eşlik eden eklem dışı bulgular, radyolojik skorlar ve tanı anında 1987 ACR-RA sınıflama kriterlerini karşılayan hasta sayısı belirlendi. Steroid ve hastalık modifiye edici antiromatizmal ilaçların (HMEAİ) dozları kaydedildi. HMEAİ tedavisinin başlangıcında ve 3. ayında hastalık aktivite skoru (DAS28-ESR) incelendi.

Bulgular: YBRA sıklığı %8.3 idi. YBRA'li hastalarda romatoid faktör pozitiflik sıklığı (%82.9), komorbid hastalık sıklığı (%77.1) ve eritrosit sedimantasyon hızı ortalama değeri (62.0±25.21 mm/saat) GBRA'li hastalardan anlamlı derecede yüksekti (sırasıyla %55, %19.9 ve 33.97±19.48) ($p<0.05$). YBRA'lı hastalar ile GBRA'lı hastalar arasında; başlangıç DAS-28-ESR değerleri, C-reaktif protein ortalama değerleri, SENS medyan değeri, anti-siklik sitrüline peptid pozitiflik sıklığı, eklem tutulum patern sıklıkları, 1987 ACR-RA sınıflandırma kriterlerini karşılayan hasta sıklığı ve steroid ile HMEAİ kullanım sıklığı açısından anlamlı farklılık yoktu ($p>0.05$). Yine YBRA ve GBRA'lı hastalar arasında tedavinin 3. ayında ölçülen DAS28-ESR değerleri ve kullanılan steroid dozları açısından farklılık yoktu ($p>0.05$).

Sonuç: YBRA ve GBRA'lı hastalarda hastalık aktivite skorları ve radyografik skorlar başta olmak üzere birçok klinik ve laboratuvar bulgu arasında farklılık yoktur.

Anahtar kelimeler: Genç Başlangıçlı Romatoid Artrit, Yaşlı Başlangıçlı Romatoid Artrit

Abstract

Objectives: To compare elderly-onset rheumatoid arthritis (EORA) patients with younger-onset rheumatoid arthritis (YORA) patients in terms of sociodemographic, clinical and radiological features, and treatment responses.

Materials and Methods: 422 rheumatoid arthritis (RA) patients were evaluated retrospectively. Patients with the age of onset of disease symptoms ≥60 were considered EORA, and those <60 were considered YORA. Sociodemographic characteristics, co-morbid diseases, laboratory values, joint involvement patterns, accompanying extra-articular findings, Simple Erosion Narrowing radiological scores (SENS) and the number of patients meeting the 1987 American College of Rheumatology-Rheumatoid Arthritis (ACR-RA) classification criteria at the time of diagnosis were evaluated. The doses of steroids and disease-modifying anti-rheumatic drugs (DMARDs) were recorded. Disease activity score with erythrocyte sedimentation rate (DAS28-ESR) at the beginning and 3rd month of DMARDs treatment were recorded.
Results: The frequency of EORA was 8.3%.The frequency of rheumatoid factor positivity(82.9%), co-morbid disease frequency (77.1%) and the mean value of erythrocyte sedimentation rate (62.0±25.21 mm/h) seen in patients with EORA were significantly higher than patients with YORA(55%,%19.9 and 33.97±19.48, respectively) ($p<0.05$).There was no significant difference between patients with EORA and patients with YORA in terms of the baseline DAS-28-ESR and C-reactive protein mean values, SENS median value, frequency of positive anti-cyclic citrullinated peptide, joint involvement frequency, frequency of meeting 1987 ACR-RA classification criteria, and frequency of steroid and DMARDs usage ($p>0.05$). There was no difference between the patients with EORA and YORA in terms of DAS28-ESR values measured at the 3rd month of treatment and steroid doses used($p>0.05$).
Conclusion: There is no difference in many clinical and laboratory findings, especially disease activity scores and radiographic scores, in patients with EORA and YORA.
Key words: Elderly-Onset Rheumatoid Arthritis, Younger-Onset Rheumatoid Arthritis

1. Introduction

Although there are no clinical findings, rheumatoid arthritis (RA) is a disease in which subclinical inflammation continues [1]. The prevalence of RA is known to be between 0.5 and 1% in the United States and northern European countries [2, 3]. Although RA can be diagnosed in all age groups and in all ethnic populations, it has an increasing prevalence with increasing age, and this frequency rises to 2% in the geriatric population [4]. The terminology is unclear; however, patients with RA whose clinical symptoms begin after age 60 or 65 are considered elderly-onset RA (EORA) [5, 6]. As life expectancy increases in developed countries, the number of people ≥60 years old is increasing rapidly; this indicates that the number of EORA patients will increase in the future. According to the UK database, the male/female ratio is reduced in EORA compared with younger-onset rheumatoid arthritis (YORA). (4/1 vs. 2/1) [7].
The aim of our study was to compare EORA and YORA patients in terms of socio demographic, clinical, laboratory, radiological characteristics, and disease activities and treatment responses.

2. Materials and Method

2.1. Population And Sample

Five hundred forty-four patients who were followed up in the rheumatology clinic and diagnosed with RA according to the 2010 American College of Rheumatology- Rheumatoid Arthritis (ACR-RA) classification criteria between March 2016 and July 2020 were retrospectively analyzed [8]. Of these patients. 3 who were pregnant, 82 with missing medical records, and 37 who had changes in disease-modifying anti-rheumatic drugs (DMARDs) treatments initiated after diagnosis were excluded from the study. The data of 422 patients with written consent were retrospectively investigated. Those at the age of onset of disease symptoms ≥60 were considered as EORA, and those <60 were considered as YORA [6]. Socio demographic data such as age (years), gender, the time elapsed between the onset of disease symptoms and the time of diagnosis (months), co morbid diseases (hypertension, diabetes mellitus, cardiovascular diseases, thyroid diseases, renal diseases, etc.) and C-reactive protein (CRP) (mg/L), erythrocyte sedimentation rate (ESR) (mm/hr.), rheumatoid factor (RF, IU/ml) and anti-cyclic citrullinated peptide (anti-CCP, U/ml) values were recorded. RF and anti-CCP tests were considered positive or negative based on laboratory reference values (laboratory reference values 0-30 IU/ml for RF, 0-4.99 U/ml for anti-CCP). The joint involvement patterns present in the physical examination of the patients at the time of diagnosis were recorded [8]. Those who had extra-articular findings (systemic vasculitis, ocular involvement, rheumatoid nodule, pulmonary involvement etc.) accompanying RA at the time of diagnosis were determined. Steroid and DMARDs (methotrexate, sulfasalazine, hydroxychloroquine and leflunomide) and treatment doses that were started after the diagnosis of RA were investigated. Disease activity score with erythrocyte sedimentation rate (DAS28-ESR) values at the time of diagnosis and at the 3rd month after the start of treatment were noted. Patients who had changes in DMARDs treatments started after diagnosis were excluded from the study. We wait a minimum of 3 months for the evaluation of the response to DMARDs treatment in our clinic. DMARDs treatment is not changed unless there is a cause such as side effects within 3 months. Steroid doses are changed only according to clinical and laboratory requirements. The steroid (prednisolone or equivalent) doses used were examined in three groups as low (<7.5 mg/day), medium (7.5-30 mg/day), and high (>30mg/day) [9]. The use of 2 or more DMARDs was called combined therapy. Radiologic scoring of hand radiographs of all patients at the initial diagnosis was performed using the Simple Erosion Narrowing Score (SENS) [10]. In addition, the frequency

of patients who met the 1987 ACR-RA classification criteria at the time of diagnosis was also determined [11].

2.1. Statistical Analysis

It was decided whether the data was normally distributed or not by evaluating the skewness and kurtosis values and normality plots [12]. Mean and standard deviation values were given for normally distributed data median and minimum-maximum values were given for non-normally distributed data. Mann Whitney U test was used to compare for non-normally distributed data, while the Student t-test was used for normally distributed data. Pearson Chi-square and Fisher Exact Test were used to determine the difference between groups. Paired Samples Test was used to evaluate DAS28-ESR levels before and at the 3rd month of the treatment. Split-plot Anova test was used to compare repeated DAS28-ESR measurements at baseline and 3rd month of DMARDs treatment in EORA and YORA patients. Significance level was accepted as $p < 0.05$. SPSS version 26 was used for statistical analysis (SPSS Inc., IBM Co., and Chicago, IL, USA).

The study protocol was approved by the Karabük University Faculty of Medicineethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results and Discussion

Four hundred twenty-two RA patients were included in the study. The mean age was 57.41±12.36 years, the mean CRP value was 24.46±14.36 mg/L, the mean ESR value was 42.45±18.60 mm/h, and the mean value of DAS28-ESR at the time of diagnosis was 4.97±1.01. While 35 (8.3%) of the patients were EORA, 387 (91.7%) were YORA.

While 27 (77.14%) of EORA patients were female and 8 (22.86%) were male, 329 (85.01%) of YORA patients were female and 58 (14.99%) were male. There was no difference in gender distribution between EORA and YORA patients (p=0.220).

Table 1 shows the socio demographic and clinical characteristics, and radiographic scores and the comparison of EORA and YORA patients at the time of diagnosis.

While the mean steroid dose started at the diagnosis in EORA patients was 9.07±3.83 mg/day, the mean steroid dose started in YORA patients was 8.60±3.95 mg/day (p=0.503). **Table 2** shows the comparison of DMARDs usage and DMARDs' doses of EORA and YORA patients started at the time of diagnosis.

While 33 (94.28%) of the patients with EORA had no extra-articular findings of RA at the time of diagnosis, 2 patients had subcutaneous rheumatoid nodules. While no extra-articular finding was detected in 369 (95.35%) patients with YORA at the time of diagnosis, there were subcutaneous rheumatoid nodule in 7 (1.81%) patients, systemic vasculitis in 1 (0.26%) patient, pulmonary involvement in 8 (2.07%) patients, and episcleritis in 2 (0.052%) patients. We found no difference between the groups in terms of extraarticular involvement (p=0.510).

While the baseline DAS28-ESR mean value of the patients with EORA was 5.13±1.20, the mean DAS28-ESR value at the 3rd month of treatment was 2.45±0.66. The baseline DAS28-ESR mean value of patients with YORA was 4.96±0.99, while the mean DAS28-ESR value at the 3rd month of treatment was 2.39±0.67. In both EORA and YORA patients, DAS28-ESR values improved significantly at the 3rd month of treatment ($p<0.001$ for each). We found no difference between patients with EORA and YORA in terms of mean DAS28-ESR value at the baseline and at the 3rd month of the treatment (p=0.424 and p=0.622, respectively).

When the DAS28-ESR values of EORA and YORA patients were compared in terms of the difference between the 3rd month of treatment and baseline, there was no significant difference between the groups (p=0.596). **Figure 1** shows the change in DAS28-ESR values of EORA and YORA patients between the 3rd month of treatment and the baseline.

In the 3rd month of DMARDs treatment, the mean dose of steroid used in EORA patients was 4.14±3.31 mg/day, and in patients with YORA, it was 4.92±2.42 mg/day (p=0.179).

3.1 Discussion

In our study, proportion of EORA was found higher than the literature. We found the gender distribution of the EORA patients and YORA patients to be similar. There was no difference in joint involvement patterns of EORA and YORA patients included in our study. When EORA and YORA patients are evaluated with the 1987 ACR-RA classification criteria, similar RA frequency is detected. In our study, RF positivity was higher in patients with EORA than in patients with YORA, while anti-CCP positivity was similar in both groups. In our study, the mean value of CRP was similar between the groups in patients with EORA and YORA, while the mean value of ESR was higher in EORA. In our study, we found no significant difference between the patients with EORA and YORA in terms of the frequency of extraarticular involvement and the median SENS scores. In our study, no significant difference was detected in steroid starting doses at the diagnosis and steroid needs at the 3rd month in patients with EORA and YORA. Also, no difference was found between the groups in terms of the use of DMARDs, their doses, and the frequency of preference for monotherapy and combined therapy. After DMARDs, the mean DAS28-ESR score improved significantly in both EORA and YORA patients. In our study, when we compared the baseline mean DAS28-ESR score in EORA and YORA patients, we could not find any difference. We did not find any difference between the mean DAS28-ESR score at the 3rd month of treatment in patients with EORA and the score of patients with YORA.

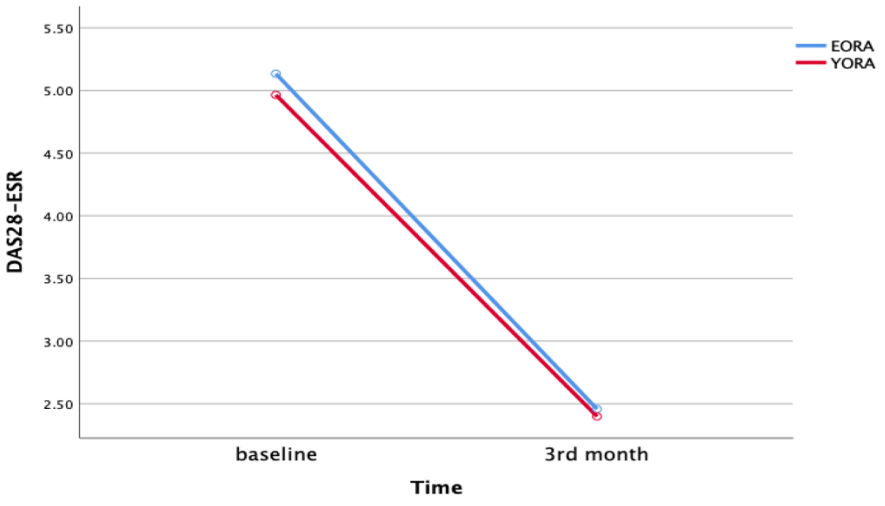
Table 1. Socio demographic and clinical characteristics, and radiographic scores and the comparison of elderly-onset rheumatoid arthritis and younger-onset rheumatoid arthritis patients at the time of diagnosis.

		EORA (n=35)	**YORA** (n=387)	**p value**
Gender n (%)	Female	27 (77,14)	329 (85,01)	0,220[a]
	Male	8 (22,86)	58 (14,99)	
Age (years) mean± SD		74.66±5.88	55.85±11.59	**<0.001[b]**
Time from the onset of disease symptoms to diagnosis (months) median (min-max)		4 (1.5-34)	5 (1.5-42)	0.102[c]
Co morbidities n (%)	Yes	27 (77.1)	77 (19.9)	**<0.001[a]**
Joint involvement pattern n (%)	Upper extremity	24 (68.6)	336 (79.6)	0,236[a]
	Lower extremity	5 (14.3)	33 (8.5)	
	Both upper and lower	6 (17.1)	42 (10.9)	
Joint involvement pattern n (%)	Small joint	28 (80,0)	350 (90,4)	0,152[a]
	Large joint	6 (17,1)	31 (8)	
	Both small and large	1 (2,9)	6 (1,6)	
Joint involvement pattern n (%)	Symmetric	25 (71.4)	261 (67,4)	0,629[a]
	Asymmetric	10 (28.6)	126 (32,6)	
Joint involvement pattern n (%)	Oligoarticular	10 (28.6)	74 (19.1)	0.180[a]
	Polyarticular	25 (71.4)	313 (80.9)	
RF positivity n (%)	Positive	29 (82.9)	213 (55)	**0,001[a]**
Anti CCP positivity n (%)	Positive	17 (48.6)	172 (44.4)	0,638[a]
CRP (mg/L) mean± SD		26.31±15.77	25.39±14.24	0.715[b]
ESR (mm/h.) mean± SD		52.46±21.53	41.54±18.07	**0,001[b]**
Initial DAS-28-ESR mean± SD		5.13±1.20	4.96±0.99	0.424[b]
SENS median(min-max)	JES	0 (0-2)	0 (0-3)	0.206[c]
	JNS	0 (0-1)	0 (0-1)	0.115[c]
	Total SENS	0 (0-3)	0 (0-3)	0.229[c]
Number of patients meeting the 1987 ACR-RA classification criteria n (%)	Meeting	30 (85,71)	310 (80,10)	0,422[a]
	Not meeting	5 (14,29)	77 (19,90)	

Significance level p<0.05, EORA: Elderly-onset rheumatoid arthritis, YORA: Younger-onset rheumatoid arthritis, n: subject number, SD: standard deviation, min:minimum, max:maximum, RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, mg: milligram, L: liter, mm: millimeter, h.: hours, DAS28-ESR: Disease activity score 28 with erythrocyte sedimentation rate, SENS: Simple Erosion Narrowing Score, JES: Joint erosion score, JNS: Joint narrowing score, a: Pearson χ^2 test, b: Student t-test, c: Mann Whitney U test, d: Fisher Exact test.

Table 2. Comparison of disease-modifying anti-rheumatic drugs usage and these drugs' doses of elderly-onset rheumatoid arthritis and younger-onset rheumatoid arthritis patients started at the time of diagnosis.				
		EORA (n=35)	**YORA** (n=387)	**p value**
Steroid usage n (%)	No	1 (2.9)	6 (1.6)	0,230[a]
	Low dose (<7.5 mg/day)	13 (37.1)	201 (51.9)	
	Medium dose (7.5-30 mg/day)	21 (60)	180 (46.5)	
Steroid dose mean± SD (mg/day)		9.07±3.83	8.60±3.95	0.503[b]
Methotrexate usage n (%)	No	3 (8.6)	11 (2.8)	0,101[c]
	Yes	32 (91.4)	376 (97.2)	
Methotrexate dose mean± SD **(**mg/week)		10.85±4.15	11.52±3.34	0.269[b]
Sulfasalazine usage n (%)	No	28 (80)	313 (81.3)	0,851[a]
	Yes	7 (20)	72 (18.7)	
Sulfasalazine dose median (min-max) (mg/day)		0 (0-2000)	0 (0-2000)	0.144[d]
Hydroxychloroquine usage n (%)	No	14 (40)	187 (48.4)	0,338[a]
	Yes	21 (60)	199 (51.6)	
Hydroxychloroquine dose mean± SD (mg/day)		200(0-400)	200 (0-400)	0.275[d]
Leflunomide usage n (%)	No	27 (77.1)	306 (79.1)	0,789[a]
	Yes	8 (22.9)	81 (20.9)	
Leflunomide dose median (min-max) **(**mg/day)		0 (0-20)	0 (0-20)	0.791[d]
Combined therapy n (%)	No	9 (25.7)	116 (30)	0.597[a]
	Yes	26 (74.3)	271 (70)	
Significance level p<0.05, EORA: Elderly-onset rheumatoid arthritis, YORA: Younger-onset rheumatoid arthritis, n: subject number, SD: standard deviation, min:minimum, max:maximum, mg: milligram, a: Pearson χ^2 test, b: Student t-test, c: Fisher Exact test, d: Mann Whitney U test				

Figure 1. The change in Disease activity score 28 with erythrocyte sedimentation rate values of elderly-onset rheumatoid arthritis and younger-onset rheumatoid arthritis patients between the 3rd month of treatment and the baseline.



DAS28-ESR: Disease activity score 28 with erythrocyte sedimentation rate**, EORA:** Elderly-onset rheumatoid arthritis**, YORA:** Younger-onset rheumatoid arthritis

The most important strength of our study is that it is the first study to compare radiological scores at the initial diagnosis in EORA and YORA patients. In addition, the high number of patients included in the study can be counted as its strength. The most important limitation of our study is that it is a single-centered study. Our work needs to be supported by multicenter national or international studies.

Although it is known that RA begins in adulthood, it can also start in childhood and at very advanced ages. 8.3% of the patients included in our study had EORA. When we look at the literature, it is seen that the frequency of RA in the geriatric population is between 2% and 2.4% [4-6]. The fact that this proportion is higher in our study compared to the literature may be due to the fact that patients now have easier access to experienced physicians dealing with rheumatology and/or the elderly population that has increased over the years.

The higher incidence of RA in women, its remission during pregnancy and its 90% recurrence after pregnancy, the different frequency and course of RA in premenopausal and postmenopausal periods, and its lower incidence in men indicate that there is a hormonal effect on this disease [7]. In our study, we found the gender distribution of patients with EORA and YORA to be similar. When we looked at the literature, similar to our study, Richter et al. [13] found the frequency of females (63%) to be similar to patients with YORA (73%). There are other studies that found the gender distribution of patients with EORA and YORA to be similar [14-16].

There was no difference in joint involvement between EORA and YORA patients included in our study. Turkcapar et al. [17] and El-Labban et al.[18] compared the demographic and clinical characteristics of EORA and YORA patients, and found that large joint involvement was higher in EORA patients than YORA, unlike our study.

In EORA patients included in our study, the proportion of those classified as RA according to the 1987 ACR-RA classification criteria was 85.71%, while this proportion was 80.10% in patients with YORA. When EORA and YORA patients are evaluated with the 1987 ACR-RA classification criteria, similar RA frequency is detected. Tamas et al. compared the 1987 ACR-RA and 2010 ACR-RA classification criteria in patients with EORA and YORA, and as a result, they showed that both criteria performed well in patients [19].

In the literature, in studies conducted in patients with EORA the information about anti-CCP antibody and RF positivity is contradictory. In some studies, the frequency of anti-CCP antibody and RF positivity was reported less in EORA than in YORA, while it was found to be similar in both groups in other studies [20-22]. Since being positive for these antibodies is an important prognostic factor, these variable antibody results also explain the different prognosis and clinical course seen in patients of different ages. In our study, RF positivity was higher in EORA patients than in YORA, while anti-CCP positivity was similar in both groups. The reason why RF positivity was detected more in EORA in our study may be due to the fact that RF increases with age. Deal et al. [21] found less RF positivity in EORA compared to YORA. Also, in support of Deal et al. [21], Turkçapar et al. [17] found RF positivity (29.03%) to be significantly lower in EORA patients than YORA (65.33%). Unlike all these, Calvo-Alen et al. [14] stated that the frequency of RF was similar in EORA and YORA patients. All these different results may be due to study designs, patient profiles included in the study (concomitant chronic hepatitis, etc.), environmental factors (air pollutants, smoking, etc.), and the effect of genetic background. Besides our study, in the study of Cho et al. [16] and Krams et al. [15], anti-CCP was evaluated. Contrary to our study, the anti-CCP value was found to be lower in the elderly in these two studies.

There are also conflicting results in studies comparing EORA patients with YORA patients in terms of acute phase reactants. In our study, the mean value of CRP was similar between the groups in patients with EORA and YORA, while the mean value of ESR was higher in EORA. This may be related to the increase in ESR with age. In some studies, higher mean CRP and ESR values were found in patients with EORA than YORA [22, 23]. In support of our study, Calvo-Alen et al. [14] and Krams et al.[15] found higher mean values of ESR in EORA patients than YORA patients, but they did not find a difference in mean values of CRP. In addition to ESR, the mean value of CRP was also higher in EORA patients than YORA [17]

In our study, no significant difference was found between EORA and YORA patients in terms of the frequency of extraarticular involvement and the median SENS scores. While Turkcapar et al. [17] detected interstitial lung disease and joint deformities more frequently in YORA than in EORA; they found rheumatoid nodules with a similar frequency. El-Labban et al. [18], on the other hand, found the rheumatoid nodules and joint erosions more frequent in YORA patients than EORA. The reason why these differences were not found in our study may be that newly diagnosed RA patients were included in our study.

The main goal in the treatment of RA is to control the disease. Although DMARDs are started for this purpose, almost all RA patients are given steroids because the onset of the effects of these treatments is long. In our study, we could not detect a significant difference in steroid starting doses at the time of diagnosis and steroid needs at the 3rd month in patients with EORA and YORA. Also, no difference was found between the groups for the use of DMARDs, their doses, and the frequency of preference for monotherapy and combined therapy. After DMARDs, the mean DAS28-ESR score improved significantly in both EORA and YORA patients.

In our study, when we compared the baseline mean DAS28-ESR score of EORA and YORA patients, we

could not find difference. We did not find difference between the mean DAS28-ESR score at the 3rd month of treatment in EORA patients and the score of YORA patients. When we look at the literature, there are different results in the literature in terms of disease activation in EORA and YORA. In the study of Cho et al. [16], DAS-28 scores in EORA and YORA patients were found to be similar, consistent with our study. Contrary to our study, Krams et al. [15] found the median value of the Simplified Disease Activity Index to be higher in EORA patients than in YORA. Similar to our study, Calvo-Alen et al. [14] found disease activation indicators to be similar in YORA and EORA.

Similar to our study, Cho et al. [16] found no difference between EORA and YORA in terms of DMARDs use, but they found steroid doses higher in YORA patients. Contrary to our results, Calvo-Alen et al. [14] detected the use of DMARDs and the use of combined DMARDs less in EORA patients than in YORA. In addition, unlike our study results, Takeda et al. [24] claimed that, low-dose use of methotrexate is more common in elderly patients.

4. Conclusion

Although rheumatoid arthritis usually starts in young-adult ages, late-onset forms can be seen with a considerable frequency. As a result, if we ignore the frequency of RF positivity, the frequency of co morbidity and the high ESR, we think that EORA is not much different from YORA in terms of clinical and laboratory features and radiological scores.

5. Acknowledgement and Disclosures: Non

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