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Favorable retention rates and safety of conventional anti-rheumatic drugs in older patients with rheumatoid arthritis

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Abstract

Physicians are challenged by the recognition and treatment of older patients with rheumatoid arthritis (RA). The aim of this case-control study was to evaluate the retention and safety of conventional disease-modifying anti-rheumatic drugs in older patients with RA.

In this observational case-control study, we assessed older patients with RA (≥65 years) who were diagnosed in 3 different rheumatology centers from Turkey. Patients were divided as to those aged ≥65 years (elderly rheumatoid arthritis [ERA]) and those aged <65 years (young rheumatoid arthritis [YRA]) at the time of conventional DMARD treatment initiation. The Mann-Whitney *U* test was used for the comparison of 2 non-normally distributed groups. The Chi-square (χ^2) test was used for categorical variables. Survival analysis were performed using the Kaplan-Meier method.

Four hundred eighteen patients with RA (296 females [71%]) were included from January 2010 to January 2018. The age of treatment onset of 190 (47%) patients was in the elderly period and they were included in the ERA group. In the analysis of drug retention rates, there was no significant difference between the ERA and YRA groups for each conventional DMARD (methotrexate 71.2% in ERA, 62.7% in YRA, $P=.817$; hydroxychloroquine 82.9% in ERA, 78.8% in YRA, $P=.899$; leflunomide 81.4% in ERA, 84.4% in YRA, $P=.205$; sulfasalazine 37.5% in ERA, 40.9% in YRA, $P=.380$). The adverse event data were also similar in both groups.

The drug retention and adverse effect rates in older patients with RA using conventional DMARDS are similar to the rates in young patients with RA.

Abbreviations: AEs = adverse events, ERA = elderly rheumatoid arthritis, ESR = erythrocyte sedimentation rate, RA = rheumatoid arthritis, TRH = Training and Research Hospital, YRA = young rheumatoid arthritis.

Keywords: conventional disease-modifying antirheumatic drugs, elderly, retention rates, rheumatoid arthritis, safety

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, mostly affecting the synovial tissue of joints and its prevalence increases with age. The proportion of older patients with RA in rheumatology practice has gained more attention because the average life expectancy is increasing, and the global population is becoming older.[1] At this point, it is important that elderly-onset RA is disputed as a distinct disease. Gonzalez-Gay et al found that early onset RA was related to DRB1/04, while elderly onset RA was associated with DRB1/01.[2] The findings of some clinical studies indicated that elderly onset RA patients had some differences clinically from the early onset patients such as large joint involvement, acute onset pattern and having marked constitutional symptoms.[3] Furthermore, the antibody positivity was reported less frequently whereas high acute phase responses were more common in elderly onset RA patients compared to the patients with early onset.[4] On the other hand, clinical and laboratory discrepancies seem to be more related to the immunopathologic changes that occur with increasing age. Such factors make the close control of treatment more challenging.[5]

Many studies interested in the effects of biologic disease-modifying anti-rheumatic drugs, an important component of modern RA therapy, on older patients with RA have been published.[6] Older patients may be less likely to receive tumor necrosis factor inhibitors due to having a greater tendency for comorbid conditions and risk of adverse events (AEs) including infections compared with younger patients.[7] In this scenario, it is very important to know whether the use of conventional DMARDs in older patients is safe, sustainable, and effective. However, the available data about the treatment of this group with advanced age using conventional DMARDs are limited.

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Today, while targeting complete remission or low disease activity, it is also important to determine the outcome of conventional DMARD treatment in older patients. The aim of this multicenter study was to evaluate the retention and the safety of each conventional DMARD (methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine) in older patients with RA compared with younger patients in clinical practice.

2. Material and methods

2.1. Patients

This retrospective study was performed in three different rheumatology centers including geriatric RA study groups in Turkey (Bakırköy Dr. Sadi Konuk Training and Research Hospital (TRH), İstanbul; Ümraniye TRH, İstanbul; Numune TRH, Ankara). Subjects with RA who fulfilled the American College of Rheumatology (ACR) criteria were enrolled from January 2010 to January 2018.[8] All patients with RA onset over 65 years of age and complete follow-up data were included in the patient group (elderly rheumatoid arthritis [ERA]) and a statistically sufficient number of patients with RA onset under 65 years of age were included in the control group (young rheumatoid arthritis [YRA]). For this group, 25 to 30 patients were randomly selected each year at the time of patient recruitment. Demographics, disease activity, laboratory tests (ie, rheumatoid factor and anti-citrullinated protein antibody), and treatment data were obtained from medical records.

The Disease Activity Score (range, 0–9.4) as calculated using the erythrocyte sedimentation rate (ESR), Physician Global Assessment (range, 0–100), and Health Assessment Questionnaire (range, 0–3) were used to evaluate disease status.[9,10] Data on extra-articular involvements and co-morbid diseases were obtained from medical records. The presence of erosion in radiographs of the hands and wrists were also recorded. Joint deformity was defined as the loss of range of motion with RA erosive lesions without any other explanatory reason for the loss. Patients who did not meet the diagnostic criteria and who were missing follow-up data were excluded.

The institutional review ethics approved this study.

2.2. Drug retention and discontinuation

The treatment data were recorded during the time patients received conventional DMARDs (methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine). Drug retention rates of each conventional DMARD were calculated for the patients who were on the drug until the drug discontinuation. Drug discontinuation was defined as stopping administration for more than 90 days. The reasons for discontinuation of conventional DMARDs were classified into AEs, ineffectiveness, disease remission, physician request, patient request, or miscellaneous.

2.3. Statistical analysis

The normality of continuous variables was investigated using the Shapiro-Wilk test. Descriptive statistics are presented as mean and standard deviation for normally distributed variables and median (and minimum maximum) for non-normally distributed variables. For the comparison of 2 normally distributed groups, Student *t* test was used. Non-parametric statistical methods were used for values with skewed distribution. For the comparison of 2 non-normally distributed groups, the Mann-Whitney *U* test was used. The Chi-square (χ^2) test was used for categorical variables and expressed as observation counts (and percentages). Survival analysis was performed using the Kaplan-Meier method. For the comparison of survival curves, the Log-Rank test was used. Cox regression was used in order to investigate the effect of confounders on drug retention rates. Statistical significance was accepted when 2-sided *P* values were lower than .05.

3. Results

3.1. Baseline characteristics

Four hundred eighteen patients with RA (296 females (71%)) with a mean age of 60.8 ± 14.0 years and total disease duration of 6.8 ± 6.7 years were included in the study. The age of disease onset of 190 (47%) patients was in the elderly period and they were included in the ERA group. The clinical characteristics of patients are shown in Table 1. The gender ratio and the rates of erosive disease were similar between the groups. There were no significant differences between the groups in terms of seropositivity. The ERA group had more active disease compared with the YRA group. The mean DAS28 scores (4.0 ± 1.4 vs 3.4 ± 1.3; $P \leq .001$), Physician Global Assessment scores (33.4 ± 24.2 vs 22.5 ± 22.9; $P \leq .001$), and Health Assessment Questionnaire scores (0.9 ± 0.8 vs 0.6 ± 0.5; $P \leq .001$) were slightly higher in the ERA group compared with the YRA group. There was a higher rate of co-morbid diseases in older patients; hypertension (57% for ERA vs 27% for YRA; $P \leq .001$), cardiovascular disease (21% for ERA vs 3% for YRA; $P \leq .001$), diabetes mellitus (26% for ERA vs 12% for YRA; $P \leq .001$), and pulmonary disease (8% for ERA vs 3% for YRA; $P \leq .015$).

Methotrexate was the most commonly used conventional DMARD, followed by hydroxychloroquine, leflunomide, and sulfasalazine in both groups. The ERA group had a lesser tendency to receiving methotrexate, hydroxychloroquine, and sulfasalazine than the YRA group (77% vs 89%, 60% vs 75%, and 17% vs 29%, respectively). During the visits, triple-conventional DMARD therapy in the ERA group was found less frequently as compared with the YRA group (3% vs 14%; $P \leq .005$), whereas mono conventional DMARD therapy was found more commonly in the ERA group (48% vs 32%; $P \leq .021$). The ERA group also had lower rates in terms of using biologic DMARDs (11% vs 25%; $P \leq .001$). These results are presented in Table 1. The ERA group also tended to use methotrexate at a lower dosage than the YRA group (12.7 ± 2.5 mg/week vs 13.7 ± 2.5 mg/week; $P \leq .009$). There was no difference between the groups according to the mean dosages of other drugs.

3.2. Drug retention and safety of conventional DMARDs

In the analysis of overall drug retention rates, there was no significant difference between the ERA and YRA groups for each conventional DMARD (methotrexate 71.2% in ERA, 62.7% in YRA, $P \leq .817$; hydroxychloroquine 82.9% in ERA, 78.8% in YRA, $P \leq .899$; leflunomide 81.4% in ERA, 84.4% in YRA, $P \leq .205$; sulfasalazine 37.5% in ERA, 40.9% in YRA, $P \leq .380$; log-rank test). The Kaplan-Meier curves of the conventional DMARDS are seen in Figure 1. The median survival time was shorter in the ERA group than in the YRA group for methotrexate (24 ± 3.5 vs 48 ± 4.6 months), for hydroxychlor-

Table 1

Demographic and clinical characteristics of patients according to the onset time of treatment.

	All patients n:418	ERA n:190	YRA n:228	*P* values
Age (mean ± SD)	60.8 ± 14.0	72.4 ± 5.1	51.0 ± 11.4	**<.001**
Female (%)	296 (71)	128 (67)	168 (74)	.096
Disease duration* (mean ± SD)	6.8 ± 6.7	5.4 ± 4.8	7.9 ± 7.7	**<.001**
Erosive disease (%)	158 (38)	75 (39)	83 (36)	.221
Joint deformity (%)	104 (25)	43 (23)	61 (27)	.251
DAS28 (mean ± SD)	3.7 ± 1.4	4.0 ± 1.4	3.4 ± 1.3	**<.001**
PhGA score (mean ± SD)	27.5 ± 24.1	33.4 ± 24.2	22.5 ± 22.9	**<.001**
HAQ score (mean ± SD)	0.7 ± 0.7	0.9 ± 0.8	0.6 ± 0.5	**<.001**
Co-morbidities				
Hypertension	169 (47)	108 (57)	61 (27)	**<.001**
Diabetes mellitus	77 (18)	50 (26)	27 (12)	**<.001**
Cardiovascular disease	45 (11)	32 (17)	6 (3)	**<.001**
Thyroid disease	40 (10)	19 (10)	21 (9)	.252
Pulmonary disease	23 (6)	16 (8)	7 (3)	**.015**
Renal disease	13 (3)	8 (4)	5 (2)	.144
Malignancy	12 (3)	5 (3)	7 (3)	.530
CRP (mg/dl)	1.5 ± 1.8	1.5 ± 1.9	1.5 ± 1.5	.126
ESR (mm/h)	37.3 ± 22.5	37.3 ± 22.2	18.0 ± 22.2	**<.001**
RF Mean ± SD	95.9 ± 148.0	111.5 ± 174.0	128.8 ± 219.6	.246
Positivity n (%)	266 (64)	121 (63)	145 (64)	.339
ACPA Mean ± SD	121.5 ± 129.9	146.4 ± 133.2	102.9 ± 124.4	.808
Positivity n (%)	237 (57)	102 (53)	135 (59)	.484
Methotrexate	344 (82)	142 (77)	202 (89)	**<.001**
Hydroxychloroquine	285 (68)	114 (60)	171 (75)	**.001**
Leflunomide	128 (31)	62 (33)	66 (29)	.240
Sulfasalazine	99 (24)	32 (17)	67 (29)	**.002**
Mono-conventional DMARD (%)	164 (39)	91 (48)	73 (32)	**.021**
Double conventional DMARD (%)	194 (46)	78 (41)	116 (51)	.156
Triple conventional DMARD (%)	38 (9)	6 (3)	32 (14)	**.005**
Biological DMARDs (%)	78 (19)	21 (11)	57 (25)	**.001**

ACPA = anti citrullinated protein antibody, COLD = Chronic obstructive lung disease, CRP = C-reactive protein, CS = corticosteroids, DAS28 = disease activity score for 28 joints, DMARDs = disease modifying anti-rheumatism drugs, ERA = elderly patients with rheumatoid arthritis, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, PhGA = physician global assessment, RF = rheumatoid factor, SD = standard deviation, YRA = young patients with rheumatoid arthritis.

* Is expressed as year.

oquine (24 ± 5.2 vs 48 ± 4.2 months), for leflunomide (24 ± 2.4 vs 45 ± 7.3 months), and for sulfasalazine (72 ± 26.1 vs 96 ± 24 months). There were no statistically significant risk factors affecting drug discontinuation according to Cox regression models with sex, age, seropositivity, and co-morbidities (Table 2).

The number of patients who discontinued conventional DMARDs for any reason during the observation period was 90 (26.3%) in the ERA group and 160 (31.9%) in the YRA group ($P = .084$). AEs were the most common discontinuation reasons in both groups (60% in ERA vs 47.2% in YRA, $P = .058$) (Table 3). The rates and types of AEs were different for each conventional DMARD (Table 4). Gastrointestinal problems related to methotrexate were the most common AEs causing drug discontinuation in both groups. In the ERA group, although the percentage of drug discontinuation due to adverse effects was found to be slightly higher for leflunomide and hydroxychloroquine, it was slightly lower for sulfasalazine. However, these results were not statistically significant. There was also no significant difference between the ERA and YRA groups in terms of the discontinuation of methotrexate due to adverse effects. Severe infection or malignancy attributed to conventional DMARDs were not observed in either group.

4. Discussion

In our study, it was demonstrated that the retention rates of conventional DMARDs in older patients with RA were comparable to those of younger patients with RA in a real-life study. Compared with the literature data, our drug retention rates of conventional DMARDs in older patients were found to be slightly higher.[11,12] Rodriquez et al reported that the discontinuation rate of leflunomide in patients with RA aged >75 years at the beginning of treatment was higher than in other patients.[12] We did not perform this analysis because leflunomide was started in only 6 patients aged >75 years. In this aspect, our study could be criticized in view of the fact that an increase in the ratio of patients aged over 75 years might influence drug retention rates.

The most important reason for the discontinuation of drugs was AEs in both groups in our study. Unlike similar studies with biologic antirheumatic drugs, severe infection or life-threatening toxicity was not observed, which is a favorable result for conventional DMARDs.[13] It was also remarkable to detect lower rates of hydroxychloroquine-related retinal toxicity in both groups. Generally, hydroxychloroquine appeared to be a well-tolerated conventional DMARD, in agreement with the literature data. Given the increased risk of comorbidities in older patients,

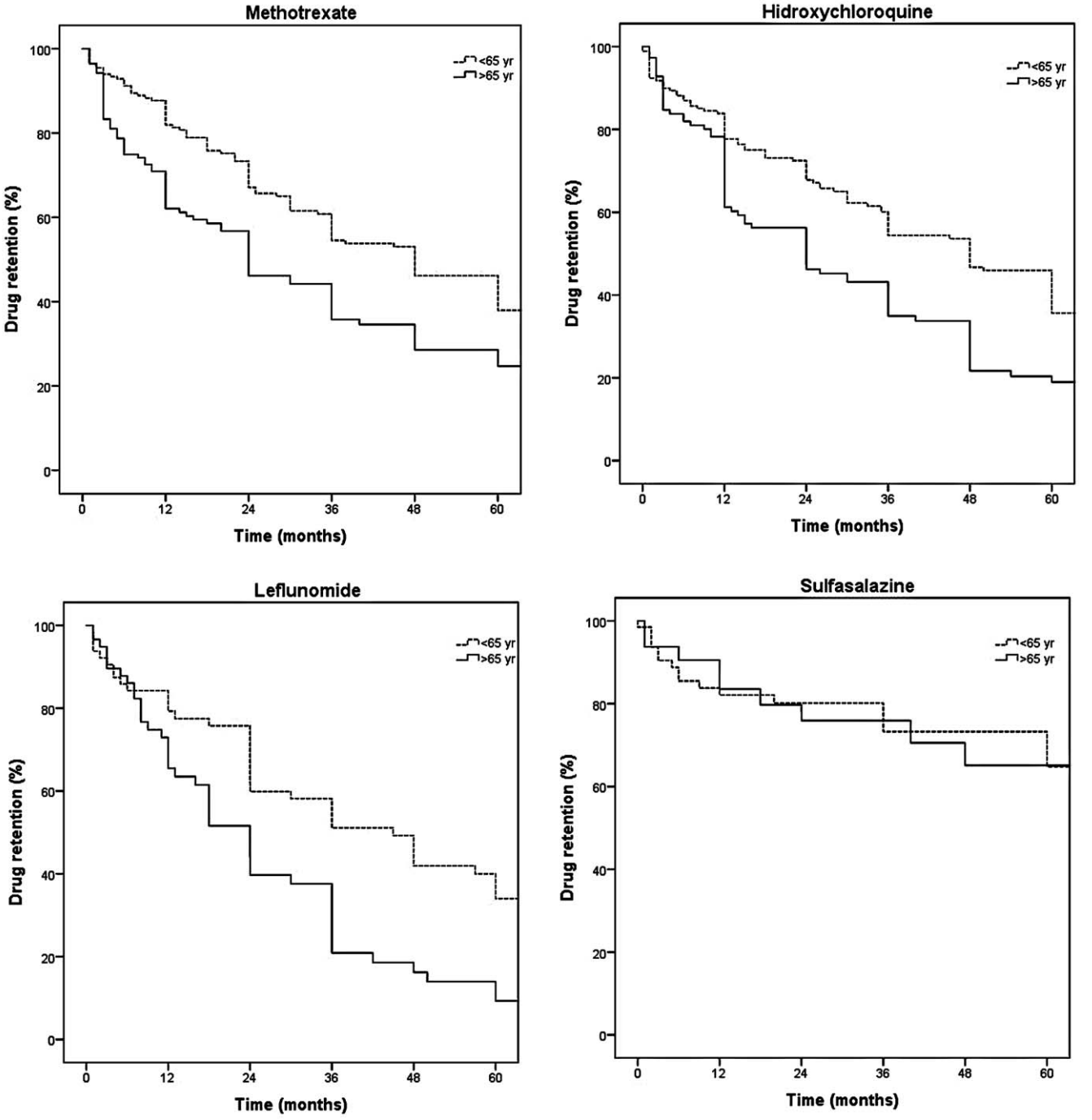


Figure 1. Persistence rates of conventional disease modifying anti-rheumatic drugs between older and younger patients with rheumatoid arthritis.

hydroxychloroquine may have an advantage over lipid prolife and insulin resistance.[14]

A previous real-life analysis study reported a non-significant difference in disease activity between older and young patients.[15] On the other hand, it seems that the older patients as a subgroup from randomized controlled trials have less active disease. This may be due to the fact that researchers are biased in patient selection to avoid difficulties in clinical management or drug toxicity. At this point, the contribution of real-life data is crucial. It should be also acknowledged that there is an inability to accurately assess disease activity in the elderly. There are insufficient studies focusing on the validation of disease activity indicators in older patients with RA.[16] However, conditions such as the low levels of depression or high levels of osteoarthritis in older patients compared with younger patients means that the disease activity scales may not accurately indicate disease activity.[17] Certainly, the reason for the active disease in older patients could be related to avoidance of physicians or patients from aggressive treatment due to concerns about the adverse effects. In support of this idea, we found that the use of combined

Table 2

Risk factors for each conventional DMARD discontinuation in RA patients.

	ERA		YRA	
	Adjusted HR 95% CI	*P*	Adjusted HR 95% CI	*P*
Methotrexate				
Sex, female	1.089 (0.514–2.306)	.824	0.692 (0.374–1.281)	.241
Age	0.959 (0.878–1.047)	.348	0.981 (0.959–1.003)	.092
Seropositivity	1.438 (0.647–3.199)	.373	0.916 (0.554–1.514)	.732
Co-morbidity	1.787 (0.855–3.733)	.123	1.146 (0.604–2.176)	.670
Hydroxychloroquine				
Sex, female	1.681 (0.555–5.092)	.359	2.265 (1.017–4.998)	.063
Age	1.040 (0.932–1.160)	.488	0.993 (0.933–1.125)	.054
Seropositivity	0.688 (0.225–2.106)	.513	1.164 (0.565–2.400)	.681
Co-morbidity	0.560 (0.194–1.614)	.283	1.308 (0.517–3.307)	.571
Leflunomide				
Sex, female	1.529 (0.266–8.806)	.634	0.978 (0.524–2.002)	.972
Age	1.073 (0.943–1.221)	.284	0.943 (0.868–1.025)	.167
Seropositivity	2.597 (0.617–10.923)	.193	0.884 (0.168–4.642)	.884
Co-morbidity	3.358 (0.699–16.146)	.130	0.295 (0.063–1.380)	.121
Sulfasalazine				
Sex, female	0.809 (0.277–2.365)	.699	1.786 (0.876–3.642)	.110
Age	0.967 (0.877–1.066)	.498	0.982 (0.946–1.019)	.339
Seropositivity	1.078 (0.310–3.750)	.905	0.906 (0.446–1.842)	.785
Co-morbidity	1.487 (0.536–4.127)	.446	1.497 (0.635–3.529)	.356

CI = confidence interval, ERA = elderly patients with rheumatoid arthritis, HR = Hazard ratio, YRA = young patients with rheumatoid arthritis.

DMARD therapy and biologic DMARD therapy in older patients with RA was lower than in young patients. Adherence to treatment in older patients might also be a specific challenge. Factors such as sociocultural characteristics, behavioral features or dependency on others (for personal care) would affect the adherence to treatment of older patients differently than the expected ways in younger patients.[18]

The retrospective analysis and inability to obtain records of the disease activity course were the most important limitations in our study. When DAS28 is calculated using ESR, it may be misleading due to finding higher levels associated with aging that increase ESR physiologically in the older age group. However, because a common result has not been agreed upon for use in different study centers, DAS28 calculations using C-reactive protein is considered appropriate. Another limitation of our study was that we could not assess corticosteroid use. In addition, our study population was relatively small, which limited the ability to evaluate different conventional DMARDs.

Table 3

The reasons for discontinuation to the conventional DMARDs, n (%).

	ERA n:350	YRA n: 506	*P* values
Reason for discontinuation			
Adverse event	54 (60)	76 (47.5)	.058
Ineffectiveness	16 (17.7)	36 (22.5)	.377
Disease remission	4 (4.4)	23 (14.3)	**.015**
Physician request	4 (4.4)	5 (3.1)	.591
Patient request	8 (8.8)	12 (7.5)	.698
Others	4 (4.4)	8 (5)	.844

ERA = elderly patients with rheumatoid arthritis, YRA = young patients with rheumatoid arthritis.

To conclude, conventional DMARDs are as important as treatment options in older patients with RA as they are in younger patients before using biologic DMARDs. Having information about the effects and safety profile of conventional DMARD therapies on older patients may provide better disease control. Although our study represents incentive data in this aspect, it is crucial to plan further prospective studies focusing on older patients treated with conventional DMARDs.

Table 4

The rates of adverse events lead to permanent discontinuation of conventional DMARDs, n (%).

	ERA	YRA	*P* values
Methotrexate			
Reason of discontinuation as AEs	33 (23.2)	51 (25.2)	.670
Gastrointestinal	26 (19.3)	44 (21.7)	.721
Hepatotoxicity	4 (2.8)	6 (2.9)	.934
Cytopenia	3 (2.1)	1 (0.5)	.168
Hydroxychloroquine			
Reason of discontinuation as AEs	9 (7.8)	5 (2.8)	.057
Retinal toxicity	5 (4.3)	2 (0.9)	.086
Gastrointestinal	3 (2.6)	2 (0.9)	.357
Hypersensitivity	1 (0.8)	1 (0.5)	.772
Leflunomide			
Reason of discontinuation as AEs	8 (12.9)	6 (9)	.490
Gastrointestinal	4 (6.5)	3 (4.5)	.635
Pruritus	3 (4.8)	2 (3.0)	.949
Hepatotoxicity	1 (1.6)	1 (1.5)	.964
Sulfasalazine			
Reason of discontinuation as AEs	4 (12.5)	14 (20.8)	.311
Gastrointestinal	4 (12.5)	12 (17.9)	.494
Hypersensitivity	–	2 (2.9)	–

AE = adverse event, ERA = elderly patients with rheumatoid arthritis, YRA = young patients with rheumatoid arthritis.

Author contributions

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