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Original Article

Elderly-onset rheumatoid arthritis receives less aggressive therapies than young-onset rheumatoid arthritis in an Argentinian cohort

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ABSTRACT

Objectives: When rheumatoid arthritis (RA) starts after the age of 60 it is called elderly-onset rheumatoid arthritis (EORA) and when it starts earlier, young-onset rheumatoid arthritis. (YORA). There are few Latin American studies that compared both groups. The objective of the study was to evaluate differences in the clinical characteristics, evolution and treatment among patients with RA with onset before or after 60 years of age.
Materials and methods: Observational study of patients with RA attended consecutively in four centers in Argentina. Sociodemographic data, comorbidities, clinical manifestations at diagnosis, presence of rheumatoid factor and/or anti-CCP (cyclic citrullinated peptide) and treatments received were collected. At the last visit, swollen and tender joints, assessment of disease activity by the patient and physician, the presence of radiographic erosions, and functional status using the HAQ-DI were recorded.
Results: 51 patients from each group were analyzed. The EORA group had a significantly higher proportion of smokers (58.8% vs. 35.3%, p = 0.029), cardiovascular history (54.9% vs. 21.6%, p = 0.001), abrupt onset (49% vs. 29.4%, p = 0.034) or with symptoms similar to PMR (19.6% vs. 0%, p = 0.001). Lower methotrexate doses were used in the EORA group: 19 mg (15–25) vs. 21.9 mg (20–25) (p = 0.0036) and more frequently did not receive bDMARDs or tsDMARDs.
Discussion and conclusions: The benefits of intensive treatment in patients with RA have been described. In this study, the use of DMARDs in the EORA group was less intensive, suggesting that advanced age constitutes a barrier in the therapeutic choice.

La artritis reumatoidea de inicio en el anciano recibe terapias menos agresivas que la artritis reumatoidea de inicio en el adulto en una cohorte Argentina

Palabras clave:
Artritis reumatoidea de inicio en el anciano
Artritis reumatoidea de inicio en el adulto
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RESUMEN

Antecedentes y objetivo: Cuando la artritis reumatoidea (AR) comienza después de los 60 años se denomina artritis reumatoidea de inicio en el anciano y cuando se inicia antes, artritis reumatoidea de inicio en el adulto. Son escasos los estudios latinoamericanos que compararon ambos grupos. El objetivo del estudio fue evaluar diferencias en las características clínicas, evolución y elección terapéutica entre los pacientes con AR de inicio antes o después de los 60 años.

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Materiales y métodos: Estudio observacional de pacientes con AR atendidos en forma consecutiva en cuatro centros de Argentina. Se recolectaron datos sociodemográficos, comorbilidades, manifestaciones clínicas al diagnóstico, presencia de factor reumatoideo y/o anti proteínas cíclicas citrulinadas (PCC) y tratamientos recibidos. En la última visita se registraron las articulaciones tumefactas, dolorosas, evaluación de la actividad de la enfermedad por el paciente y el médico, la presencia de erosiones radiográficas y el estado funcional mediante el HAQ-DI.
Resultados: Se analizaron 51 pacientes de cada grupo. El grupo de AR del anciano tuvo significativamente mayor proporción de fumadores (58,8% vs. 35,3%, p = 0,029), de antecedentes cardiovasculares (54,9% vs. 21,6%, p = 0,001), inicio abrupto (49% vs. 29,4%, p = 0,034) o con síntomas similares a la PMR (19,6% vs. 0%, p = 0,001), menores dosis de metotrexate: 19 mg (15–25) vs. 21,9 mg (20–25) (p = 0,0036) y con mayor frecuencia no recibieron FAMEb o FAMEsd.
Discusión y conclusiones: Se han descrito los beneficios del tratamiento intensivo en paciente con AR. En este trabajo, el empleo de FAME en el grupo de AR de inicio en el anciano fue menos intensivo, sugiriendo que la edad avanzada constituye una barrera en la elección terapéutica.

Introduction

Rheumatoid arthritis (RA), a systemic autoimmune disease that primarily affects synovial tissue, is associated with structural damage, reduced physical function, compromised quality of life, and premature death.[1,2] When the disease begins after the age of 60, it is termed adult-onset or late-onset rheumatoid arthritis, and when it starts earlier, adult-onset rheumatoid arthritis.[3]

The prevalence of RA in people over 60 years of age is 2%, and its onset in the elderly accounts for 10–33% of all RA.[3,4] An increase in the number of cases is now expected due to longer life expectancy. Onset RA in the elderly often has an acute-onset form, constitutional symptoms, markers of inflammation, polymyalgia rheumatica-like (PMR) involvement, and lower rheumatoid factor positivity.[2,5] Due to the effect of age and RA on the immunological ageing process, these patients have more comorbidities, higher erythrocyte sedimentation rate (ESR) values, and functional impairment, as measured by the *Health Assessment Questionnaire-disability index* (HAQ-DI).[2,6]

In routine practice, the therapeutic approach in elderly-onset RA is usually different from that of the adult-onset group,[6] possibly due to fear of potential adverse effects due to comorbidities and their under-representation in clinical trials. The use of corticosteroids is more frequent and given at higher doses in elderly-onset RA, whereas conventional synthetic disease-modifying drugs (csDMARDs) are usually used at lower doses than in the adult-onset group.[1] The use of targeted synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs) is less common.[7]

There are few Latin American studies that have compared elderly-onset RA with that of adult-onset.[8,9] The aim of this study was to explore differences in clinical characteristics, outcome, and therapeutic choice between patients with RA-onset before or after the age of 60 years in four medical centres in Argentina.

Materials and methods

An observational study was conducted in a consecutive sample of patients diagnosed with RA, treated from August 1st, 2021 to March 31st, 2022 in the rheumatology unit of four general hospitals in Argentina, located in an urban setting. Patients older than 18 years of age with symptom onset after January 1st, 2010, after which bDMARDs were available in the country, and who met the classification criteria of the American College of Rheumatology (*ACR) and the* European Alliance of Associations for Rheumatology (EULAR) 2010 for RA[10] were included. Patients with overlap with another connective tissue disease, with the exception of Sjögren's syndrome, were excluded. Patients signed the informed consent; the protocol was approved by the Teaching and Ethics committees of the participating centres and was conducted in compliance with the guidelines stipulated under Law 3301/09 of the Ministry of Health of the City of Buenos Aires government and the Declaration of Helsinki.

Depending on the age of disease onset, before or after 60 years, patients were classified into adult-onset RA and elderly-onset RA, respectively. Medical records were reviewed to collect sociodemographic data, comorbidities, clinical manifestations at the time of diagnosis, and the presence of rheumatoid factor and/or anti-cyclic citrullinated proteins (anti-CCPs). GLADEL's definitions for ethnicity were used.[11] Diagnostic delay was defined as the time elapsed between the onset of symptoms and the time of diagnosis, while the duration of disease was defined as the time between the date of diagnosis and the date of the last evaluation.

Treatments received from date of diagnosis were reported in terms of the use of csDMARDs (methotrexate, leflunomide, sulfasalazine); DMARDs (tofacitinib, baricitinib, upadacitinib), and bAMARDs (adalimumab, certolizumab, etanercept, golimumab, abatacept, tocilizumab, or rituximab).

At the time of the last visit, the number of swollen and painful joints and activity of the disease, according to the patient and physician, were recorded using a numerical visual analogue scale (VAS) from 0 to 10. The presence of extra-articular manifestations, radiographical erosions, and functional status were evaluated using HAQ-DI. Remission was defined as the absence of active disease as measured either by the *Disease Activity Score* (DAS 28) $\leq$2.6 or the Clinical Disease Activity Index (CDAI) $\leq$2.8 or the *Simplified Disease Activity Index (SDAI)* $\leq$3.3, depending on the physician treating the case. Time was set aside until this was achieved.

Results were reported as a percentage for categorical variables and as mean $\pm$ standard deviation or median and interquartile range (IQR) for numerical variables. Chi-square or Fisher's exact tests, as appropriate, were used to compare proportions. To compare numerical variables, the Student's test or the Mann–Whitney U test was used, depending on the distribution of the variable. To test normality, the Shapiro Wilk test was used while multiple logistic regression was utilised to adjust dichotomous outcome variable relationships. In all cases, a value of $p < 0.05$ was considered significant. The analysis was performed using the Stata 16.1 programme (StataCorp, Texas, USA).

Results

A total of 102 patients with RA were analysed: 51 with adult-onset RA and 51 with elderly-onset RA. The Lanari Institute included 26 patients from each group and the Ángel Cruz Padilla Hospital 10 from each group, while the Tornú Hospital included 5 with adult-onset RA and 12 with RA in the elderly, while the Institute of Psychophysical Rehabilitation included 11 and 2 patients, respectively. Significant differences were found in the ethnic group with the highest proportion of whites, attended at the Lanari Institute (46.1%); native Americans at the Ángel Cruz Padilla Hospital (50%), and the mixed-race group at the Institute of Psychophysical Rehabilitation (84%) and the Tornú Hospital (71%), with p = 0.000. No significant differences were found in the distribution by gender between the centres.

When analysing the 102 patients, the mean age at diagnosis was 56 ± 15.2 years. The median delay in diagnosis was 4.9 (2.1–7.6) months. Table 1 presents the comparison of demographic data and comorbidities between the groups.

Significant differences were found in ethnicity, with a higher proportion of native Americans in the adult-onset RA group and whites in the elderly-onset RA group. The latter had a significantly higher proportion of smokers and patients with a cardiovascular history. The diagnostic delay was slightly longer in the elderly-onset RA group but did not reach statistical significance.

Table 2 compares the clinical and serological characteristics between the two groups at the time of diagnosis.

The elderly-onset RA group had a higher proportion of patients with abrupt onset and PMR-like symptoms. The adult-onset group had a higher frequency of rheumatoid factor and anti-CCP positives, but the difference did not reach statistical significance.

Table 3 shows the clinical characteristics at the last visit for both groups. No significant differences were found between the groups.

HAQ values at the last visit were similar in both groups, and no significant differences were observed after adjusting for age at last visit, age at diagnosis, or duration of disease in the multivariate analysis. Table 4 presents the treatments received. The use of tofacitinib was significantly more frequent in the adult-onset RA group.

The use of csDMARDs was similar in the two groups: 48 patients (94.1%) in the adult-onset RA group and 46 (90.2%) in the elderly-onset group (p = 0.715). There were significant differences in the maximum dose of methotrexate used, 21.9 mg (20–25) in the adult-onset RA group vs. 19 mg (15–25) in the elderly-onset group (p = .0036).

Table 5 shows the use of bDMARDs or tsDMARDs.

Treatment-associated adverse events were reported in 16 patients in the adult-onset RA group and 9 in the elderly-onset group (p = .107). Increased transaminases were the most frequent event in both groups.

Discussion

Elderly-onset RA, in its initial description, was considered a benign form of RA in terms of achieving remission or low disease activity and developing less structural damage.[12] This evidence was obtained prior to the development of the 1987 ACR classification criteria, where some patients might respond to other diagnoses, such as PMR.[13] Over time, with comparative studies of elderly-onset RA vs. adult-onset, a similar clinical evolution[8,14,15] or an even more severe one was observed in the group of elderly-onset RA.[7,16–18] The results of the present cohort are consistent with these latter observations, since both the percentage of patients who achieved remission and the presence of erosions were similar in both groups.

RA is one of the chronic autoimmune diseases that predominates in women. In the case of elderly-onset RA, a more even gender distribution has been described, with a female-to-male ratio of 1.5–2:1 compared to 4–4.5:1 in other age groups.[3,19–21] In this study, there was a majority of women in both groups, with no differences in the female-male ratio.[22] With respect to ethnicity, there was a higher proportion of native Americans in the adult-onset RA group and whites in the elderly-onset group. This data is not comparable with what has been published so far in other studies on the South American population, since either a different classification for ethnicity was used or this data was not reported.[8,9]

Regarding differences in clinical presentation at diagnosis, between the groups of elderly-onset RA and adult-onset, in this study the adult-onset group presented abrupt onset more frequently, similar to what has been reported by other authors.[12,14,18] Although no difference was observed in the frequency of fever, weight loss, and night sweats as the form of presentation in this series, other authors had reported these more frequently in the group of elderly-onset RA.[23–25] Patients with elderly-onset RA may present with a clinical picture similar to PMR,[14,21] characterised by pain and stiffness in the shoulder and pelvic girdle with elevated acute phase reagents. Polymyalgia rheumatica is more common after age 50 and responds well to low doses of corticosteroids. Both categories can have arthritis in the hands. These similarities mean that the diagnosis of RA or PMR can be reached in the same patient at different times, depending on the clinical expression of the disease, and patients who are initially considered to have a diagnosis of PMR are finally diagnosed with elderly-onset RA after a longer follow-up period.[21] In this study, this form of presentation, as described, was more frequent in the elderly-onset RA group.

HAQ is used in daily practice to assess performance status in patients with RA. Although there is no consensus as regards what value is considered relevant disability, a score of ≥1.0 would be indicative of significant disability.[26] However, it has been reported that the value of HAQ increases with age and with the duration of the disease, however it is not known whether the age of onset of RA affects its outcome.[27] Jaime Calvo-Alén et al.[22] reported greater functional loss and greater anatomical damage in patients with adult-onset RA, in whom age of onset had an independent effect on both outcomes, although their condition was treated less aggressively. Disparate results were obtained in the literature, some showing worse HAQ results in the group with elderly-onset RA[22,27] and others better.[8,15] In this study, no differences were observed in the HAQ questionnaire at the last visit, when comparing groups of elderly-onset and adult-onset RA, or after adjusting for age at diagnosis, duration of disease, and age at the last visit.

The treatment of RA aims to control clinical manifestations, prevent structural damage, preserve function, and reduce excess mortality.[2] DMARDs are started as soon as the diagnosis of RA is reached, with the aim of achieving remission or, if this is not possible, limiting this to low disease activity, and the patient is monitored with visits every 1–3 months.[28] Delays in starting treatment with DMARDs are associated with increased joint inflammation and destruction, with a negative impact on physical function and the development of complications. Although the therapies available for RA have similar efficacy and safety in both young and long-lived patients,[29,30] in practice the elderly-onset group receives less aggressive therapies with steroids and monotherapy with low-dose methotrexate or other DMARDs.[30] Consistent with

Table 1
Demographic characteristics and comorbidities.

	Adult onset (n = 51)	Elderly onset (n = 51)	p
Female, n (%)	40 (78.4)	39 (76.5)	.813
Age at diagnosis, mean ± SD	43.4 ± 10.1	68.7 ± 6.4	–
Diagnostic delay (months). median (IQR)	4.8 (1.8–7.4)	5.46 (2.1–8.1)	.7709
Ethnic group, n (%)			
Whites	12 (23.5)	22 (43.1)	.004
Mixed race	24 (47.1)	25 (49)	
Native Americans	15 (29.4)	3 (5.8)	
Asians	0	1 (1.9)	
Years of education. median (IQR)	12 (12–16)	12 (8–16)	.1075
Comorbidities, n (%)			
Smokers	18 (35.3)	30 (58.8)	.029
Dislipemia	11 (21.6)	13 (25.5)	.816
Cardiovascular (HT, HF, arrhythmias, coronary artery disease, cerebrovascular disease)	11 (21.6)	28 (54.9)	.001
Diabetes	3 (5.9)	6 (11.8)	.487
Impaired kidney function	1 (1.9)	1 (1.9)	1.000
Neoplasm	0	4 (7.8)	.118

SD: Standard Deviation; HT: Hypertension; HF: Heart failure; IQR: Interquartile Range.

Table 2
Clinical and serological characteristics at diagnosis.

Diagnostic features	Adult onset (n = 51)	Elderly onset (n = 51)	p
Abrupt onset, n (%)	15 (29.4)	25 (49)	.034
PMR symptoms, n (%)	0	10 (19.6)	.001
Fever, n (%)	1 (1.9)	0	.500
Weight loss, n (%)	6 (11.8)	3 (5.9)	.487
Night sweats, n (%)	2 (3.9)	2 (3.9)	1.000
Morning Stiffness, n (%)	39 (75)	35 (70)	.659
Anaemia, n (%)	14 (27.5)	14 (27.4)	1.000
Reumatoid factor, n (%)	43 (84.3)	38 (74.5)	.327
Anti-CCP, n (%)	39 (76.5)	34 (66.7)	.380

CC: Cyclic citrullinated proteins; PMR: Polymyalgia rheumatica.

Table 3
Clinical characteristics at last visit.

Characteristics assessed at last visit	Adult onset (n = 51)	Elderly onset (n = 51)	p
Duration of illness (months). median (IQR)	63 (20–97)	35 (15–94)	.2071
Age at last visit, average ± SD	48.3 ± 10.7	72.7 ± 6.2	.0000
Extra-articular manifestations, n (%)			
Nodules	4	4	1.00
Raynaud's phenomenon	2	0	.495
Fatigue	8	6	.775
Associated Sjögren's syndrome	4	4	1.00
Episcleritis	1	1	1.00
Scleritis	1	1	1.00
Skin ulcers	0	1	1.00
Interstitial lung disease	1	4	.362
Pericarditis	1	0	1.00
Erosions, n (%)	27 (52.9)	21 (41.2)	.234
Have you ever reached remission? n (%)	33 (64.7)	36 (70.6)	.525
Remission at last visit	21 (41.2)	26 (50.9)	.427
Painful joints. median (IQR)	1 (0–4)	0 (0–2)	.1861
Swollen joints. median (IQR)	1 (0–4)	0 (0–1)	.0225
Medical VAS (0–10), median (IQR)	2 (0–6)	1 (0–5)	.5420
Patient's VAS (0–10), median (IQR)	3 (1–5)	3 (1–5)	.8210
HAQ, median (IQR)	0.62 (0–1.25)	0.5 (1.125–1.187)	.9924
HAQ > 1, n (%)	15 (29.4)	13 (25.5)	.657[a]

VAS: Analogous Visual Scale; HAQ: *Health Assessment Questionnaire*; IQR: Interquartile Range.
[a] Comparison continued to be non-significant when adjusting for age at last visit. Age at diagnosis and duration of disease with multiple or multivariate logistic regression.

Table 4
Treatments received.

Treatments received	Adult onset (n = 51)	Elderly onset (n = 51)	p
Corticosteroids, n	44	48	.183
Hydroxychloroquine, n	17	11	.183
Methotrexate, n	48	46	.461
Leflunomide, n	25	17	.108
Sulfasalazine, n	6	1	.050
Adalimumab, n	6	3	.295
Etanercept, n	6	1	.050

Table 5
Treatment with bDMARDs or tsDMARDs.

Treatments received	Adult onset (n = 51)	Elderly onset (n = 51)	p-value
Without bDMARDs or tsDMARDs, n (%)	23 (45.1)	44 (86.3)	< .001
One only, n (%)	19 (37.2)	2 (3.9)	
Two or more bDMARDs or tsDMARDs, n (%)	9 (17.7)	5 (9.8)	

other studies, in this study the rates of use of bDMARDs or tsDMARDs and maximum doses of methotrexate were lower in the elderly-onset RA group. This suggests that advanced age constitutes a barrier to early and effective treatment of RA, as it determines the therapeutic selection of the rheumatologist, possibly due to fear of adverse events, mainly infections.

The percentage of patients who achieved remission at some point in their disease or who were in remission at the last visit was similar in both groups, despite patients with adult-onset RA having received less intensive treatment. One of the limitations of this study is that the cumulative dose of steroids or the dose at the time of the last visit is not available. This shortcoming should be considered when analysing remission rates.

The main limitation of the study is the retrospective approach, and although most of the STROBE criteria for observational studies were met, we can identify other limitations, such as the small sample size and not having used a probability sampling technique. However, with a consecutive sample, an attempt was made to incorporate the entire population accessible to the researchers. In addition, there were differences between medical centres as regards the proportion of patients included by each centre and also in the case of ethnicity. A prospective study would provide more information, including data on complications and mortality. However, given that the literature on this topic in South America is scanty, the contribution to the knowledge of elderly-onset RA is considered valuable.

Conclusions

The available information on the clinical characteristics, evolution and prognosis of patients with elderly-onset RA has evolved in recent decades from its initial description as a benign condition to the current one as a form that is similar to adult-onset RA.[8,12,14,15] The benefits of early treatment in patients with RA have been described. In this study, the use of DMARDs in the elderly-onset RA group was less intensive, suggesting that advanced age constitutes a barrier to therapeutic choice. Prospective studies with evaluation of complications and mortality are required to assess whether the approach of patients with elderly-onset RA should be similar to that of other patients with RA.

Conflict of interest

The authors declare no conflict of interest.

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