ORIGINAL ARTICLE

Thoughts and considerations on Elderly onset Rheumatoid Arthritis: A case-control study of a North African population

Réflexions et considérations sur la polyarthrite rhumatoïde chez les sujets âgés: Une étude cas-témoins dans une population Nord-Africaine

Kaouther Maatallah, Ines Cherif, Hanene Ferjani, Wafa Triki, Dorra Ben Nessib, Dhia Kaffel, Wafa Hamdi

Rheumatology department, Kassab orthopedics institute, Ksar Saïd, Tunisia. Faculty of medicine of Tunis, University Tunis el Manar, Tunisia

Abstract

Introduction: Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease, and elderly onset RA starting after age 65 (EORA) is on the rise constituting approximately one-third of RA cases.
Aim: To identify the clinical and therapeutic specificities of EORA.
Methods: This was a cross-sectional case-control study of 224 RA patients (recruitment was done over a 30-month period between 2018 and 2021). Two groups were evaluated:
Elderly onset rheumatoid arthritis (EORA): patients in whom the disease started after the age of 65 and the young-onset rheumatoid arthritis (YORA) control group: patients with disease onset before the age of 65. We collected the clinical characteristics and we compared the therapeutic modalities between both groups:
Results: Our study included 59 patients in the EORA group and 165 patients in the YORA group. The onset of RA in both groups was predominantly progressive and polyarticular. However, in the EORA group, rhizomelic involvement and abrupt onset were significantly more frequent than in the YORA group, with respectively (ORa=4.8 CI=1.5-15.6; p<0.01) and (ORa=5.1 CI=1.8-14; p<0.01). Methotrexate (MTX) was the most frequently used background treatment in both groups. There was no significant difference between the two groups in the prescription of the other conventional DMARDs. Adverse events were more frequently found in the EORA group (ORa=4.7 CI=1.3-16.4, p<0.05) and consisted mainly of gastrointestinal intolerance. Rehabilitation was advocated in 6.7% of the EORA group versus 16.9% of the YORA group, with a significant difference (ORa=4.73 [1.36-16.47), p=0.02).
Conclusion: In EORA patients, therapeutic modalities overlapped with those for young-onset RA. Therapeutic decisions should be carried out without depriving EORA patients with good biological age from advanced and auspicious treatment.

Key words: Rheumatoid arthritis, Elderly RA, Late-onset RA, EORA, LORA, YORA.

Résumé

Objectifs: Cette étude visait à identifier les spécificités cliniques et thérapeutiques de la polyarthrite rhumatoïde (PR) chez les patients âgés.
Méthodes: Nous avons réalisé une étude transversale cas-témoins sur 224 patients atteints de PR, recrutés sur une période de 30 mois (2018-2021). Deux groupes ont été constitués :
• PR du sujet âgé (PRSA) : début de la maladie après 65 ans.
• PR du sujet jeune (PRSJ) : début de la maladie avant 65 ans (groupe contrôle).
Les données cliniques et les traitements ont été recueillis et comparés entre ces deux groupes.
Résultats: L'étude a inclus 59 patients PRSA et 165 patients PRSJ. Dans les deux groupes, la PR débutait principalement de façon progressive et polyarticulaire. Cependant, les atteintes rhizoméliques et les débuts brutaux étaient significativement plus fréquents chez les PRSA (ORa = 4,8 IC = 1,5-15,6 ; p < 0,01 et ORa = 5,1 IC = 1,8-14 ; p < 0,01).
Le méthotrexate restait le traitement de fond le plus utilisé dans les deux groupes. Aucune différence significative n'a été observée pour les autres traitements conventionnels. Les effets secondaires, principalement gastro-intestinaux, étaient plus fréquents chez les PRSA (ORa = 4,7 IC = 1,3-16,4 ; p < 0,05). La réhabilitation était moins souvent recommandée chez les PRSA (6,7 %) comparé aux PRSJ (16,9 %) (p = 0,02).
Conclusion: Les traitements des PRSA sont similaires à ceux des PRSJ. Les patients âgés en bon état général ne doivent pas être privés de thérapies innovantes.

Mots clés: Polyarthrite rhumatoïde, Rhumatologie, Gériatrie, PRSA

Correspondance
Ines Cherif
Rheumatology department, Kassab orthopedics institute, Ksar Saïd, Tunisia. Faculty of medicine of Tunis, University Tunis el Manar, Tunisia
Email: ines.cherif@aol.fr

LA TUNISIE MEDICALE-2025; Vol 103 (06): 691-697 DOI: 10.62438/tunismed.v103i6.5741

Advances in Knowledge

1. Clinical Characteristics of EORA: The study identifies that EORA often presents with rhizomelic involvement and abrupt onset, which is significantly more frequent compared to YORA.
2. Therapeutic Modalities: Methotrexate remains the most commonly used treatment in both EORA and YORA groups, indicating its broad applicability.
3. Adverse Events: EORA patients experience higher rates of adverse events, particularly gastrointestinal intolerance, highlighting the need for careful management.
4. Rehabilitation Needs: Rehabilitation is less frequently advocated for EORA patients compared to YORA, suggesting potential differences in post-treatment care requirements.

Application to Patient Care

1. Tailored Treatment Plans: Clinicians should consider the distinct clinical presentations of EORA, such as rhizomelic involvement and abrupt onset, when diagnosing and treating elderly patients.
2. Methotrexate Usage: The common use of Methotrexate in both EORA and YORA patients supports its continued use as a first-line treatment across different age groups.
3. Managing Adverse Events: Increased vigilance for gastrointestinal side effects in EORA patients is crucial, necessitating proactive management strategies.
4. Rehabilitation Considerations: The significant difference in rehabilitation advocacy suggests that tailored rehabilitation protocols may be beneficial for EORA patients to improve outcomes.

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic disease.
It can affect patients of both genders and at any age. Recent studies have shown that RA starting after the age of 65 is becoming increasingly common (1).
In fact, the increased life expectancy worldwide puts us in front of an inevitable framework: the aging of the population with increased frailty and changes in the immune system known as immunosenescence. This leads to a risk of autoreactivity and the occurrence of certain immune-mediated diseases, such as RA. (2)
Two forms of RA can, therefore, be distinguished. (3) The late-onset form is defined as a disease whose symptoms begin after the age of 65 years called EORA (elderly onset rheumatoid arthritis), and the early-onset form is described as a disease whose symptoms begin before the age of 65 years called YORA (young-onset rheumatoid arthritis), although some research have set the threshold to 60 years old. (4)
The clinical expression and the implications of RA in the elderly are poorly studied as clinical trials often consider advanced age among exclusion criteria.
While modern therapeutic strategies in RA such as Treat To Target (T2T) are beginning to gain foothold and recognition, they cannot always be implemented in elderly patients. This may be due to the caregiver's fear of administering the same immunosuppressants to elderly patients with greater comorbidities and more frequent polypharmacy.(2,5) This attitude, however, is not always endorsed by scientific evidence and background treatments for RA have shown the same efficacy and safety overall, regardless of age.(6) Furthermore, data from the German biologics register RABBIT showed that effective control of disease activity in RA decreases mortality in patients of all ages and that DMARDS have potential benefits in this regard.(7)
In such wise, EORA still needs to be appropriately studied and clinical and therapeutic approaches should be suggested to provide the finest care for patients.
Thus, our main objectives were to determine the clinical, biological, immunological, and radiological particularities of patients with RA starting at an advanced age and identify the therapeutic specificities of this form of RA.

Methods

Study design

This was a cross-sectional case-control study of 224 RA patients. Patients were consecutively included during hospitalization in the rheumatology department. Recruitment was done over a 30-month period between 2018 and 2021.

Study setting and population

Patients with RA meeting EULAR 2010 criteria were included.(8)Two groups were evaluated:
The Elderly onset rheumatoid arthritis (EORA) study group (formed by patients in whom the disease started after the age of 65) and the young-onset rheumatoid arthritis (YORA) control group (patients with disease onset before the age of 65). We did not include in this study patients in whom the date of disease onset was undetermined or difficult to determine. Patients with chronic inflammatory rheumatism or connective tissue diseases associated with RA were also not included.

Data collection and variables

We collected the clinical characteristics of the patients (age of patients, gender, co-morbidities), disease characteristics: age of onset and disease duration, initial clinical presentation, the immunological profile of patients, biological profile (ESR: erythrocyte sedimentation rate, CRP: c-reactive protein). We evaluated the clinical and biological activity of the disease using the composite Disease activity scores DAS28 CRP and DAS28 ESR, as well as the functional impact evaluated by the HAQ (Health Assessment Questionnaire).
X-rays of the hands and wrists, forefeet, pelvis, and cervical spine in hyperflexion and bone mineral densities of the two groups were compared as well as the therapeutic modalities: analgesic, steroids use, Nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (cs DMARDs), biological DMARDs (bDMARDs), physical and surgical treatments. Adverse events and drug tolerance were assessed.
Consent was obtained for experimentation with human participants.
Our Ethical committee approved this study.

Statistics

All data were analyzed using SPSS Version 18 for Windows. Simple and relative frequencies were calculated for qualitative variables. Means, medians, standard deviations, and extreme values were calculated for quantitative variables.

The comparison of 2 means on independent series was carried out by the Student's t-test for independent series. Comparisons of percentages on independent series were performed by Pearson's chi-square test. Comparison of qualitative variables was performed by the Chi 2 test. The Yates correction was used if any of the four boxes had a patient count≥3 and<5 and the Fisher test if any of the four boxes had a patient count≤2.

The Mantel-Haenszel test was used to identify the specificities of late-onset RA independently of the disease progression's duration, and the adjusted odds ratios with a 95% confidence interval were calculated.

Results

Clinical characteristics of patients in EORA and YORA groups

The EORA study group included 59 patients and the YORA group included 165 patients. Sixty-four percent of the patients in the EORA group had co-morbidities at the time of the study, compared to only sixteen percent in the YORA group. The difference was statistically significant (p<0.001). Sociodemographic and clinical characteristics of patients in both groups are reported in table I.

Table 1. Sociodemographic and clinical characteristics of patients in the EORA and YORA groups

Parameters		EORA	YORA	P
Age (years, mean±SD)		71.5 ± 5.9	53.1± 10	**<0.001**
Sex ratio (F/M)		0.3	0.2	0.2
Tobacco use (%)		18.6	17	0.7
BMI (kg/m2)		26.5±4.5	25.6±4.6	0.12
Age of menopause (years, mean±SD)		50 ± 6.1	48.46 ±4.9	0.15
Comorbidities (%)	Cardiovascular diseases	29 (48.8)	7 (4.2)	**<0.001**
	Diabetes	15 (25.4)	14 (8.4)	**0.001**
	Other *(asthma, surgical history...)*	6 (10)	2 (1.2)	**0.005**

EORA: Elderly onset rheumatoid arthritis, **YORA**: Yong onset rheumatoid arthritis, **BMI**: Body mass, **index F**: female, **M**: male , **SD**: Standard deviation

Disease characteristics in EORA and YORA groups

Clinical, biological, immunological, and radiological characteristics

The mean disease duration of RA in the EORA group was 3 ± 2.9 years [1-14], while it was 8.2 ± 8 years [1-37] in the YORA group (p<0.001). there was a statistically significant difference between the two groups regarding the presence of deterioration of general condition (p=0.02), the abrupt onset (p<0,001), the initial articular manifestation (p=0.01), the GPA (p<0,001) and the mean value of Health Assessment Questionnaire (HAQ) (p<0,001). Table II summarizes the disease-related parameters in the EORA and YORA groups.

Table 2. Summary table of results for disease-related parameters in the EORA and YORA groups.

Parameters			EORA	YORA	P
Age of onset (years)			69±5.01	44.6±10.7	***<0.001***
Disease's duration (years)			3±2.9	8.2±8	***<0.001***
Immunological data Nb(%)	RF		44 (74.5)	114 (69)	***0.4***
	ACPA		37 (62.7)	116 (70.3)	***0.2***
	ANA		3 (5)	7 (4.2)	***0.6***
Initial clinical presentation (%)	General symptoms		23.7	11.5	***0.02***
	Onset (progressive / abrupt)		77.9/22.1	94.6/5.4	***<0.001***
	Initial articular manifestation	Polyarticular	81.4	92.7	**0.01**
		Rhizomelic	15.2	3.6	***0.006***
Clinical assessment	Night awakenings (n)		3.8±12.8	1.5±1.4	0.18
	Morning stiffness(mn)		65.6±72.5	64.4±51.8	*0.8*
	Painful joints (n)		13.2±8.8	11.2±8.8	*0.14*
	Swollen joints (n)		5±4.2	4.8±4.2	*0.7*
	GPA		61.3±16.1	37.6±13.1	***<0.001***
	HAQ score		2.1±0.8	1±0.9	***<0.001***
DAS 28	CRP		5.3±1.1	5.1±1.2	0.6
	ESR		5.6±1.1	5.3±1.3	*0.13*
Total SHARP score			117.2±75.5	113.7±105.4	*0.7*
densitometric profile (%)	Severe osteoporosis		32.2	16.3	***0.01***
	Osteoporosis		44	19.3	***<0,001***

EORA : Elderly onset rhumatoïd arthritis, **YORA** : Yong onset rhumatoïd arthritis, **GPA** : global pathology assessment, **ESR** : erythrocyte sedimentation rate, **CRP** : C-reactive protein, **hb** : hemoglobin assay, **DAS** : Disease Activity Score, Nb: number of patients, **RF**: rheumatoid factor, **ACPA**: anti-citrullinated Peptide Antibodies, **ANA**: Antinuclear antibody.

Therapeutic modalities

The distribution of patients in both groups according to corticosteroids, background treatment prescription modalities, and occurrence of adverse events is reported in table III.

There were no significant differences in the treatment modalities between the two groups except for the combination of methotrexate and biotherapy; n=0 in the EORA group compared to n=14 (8.4%) in the YORA group, p=0,02. The frequency of adverse events was significantly higher in the EORA group, p=0.006.

Table 3. Distribution of patients in the EORA and YORA groups according to corticosteroids, background treatment prescription modalities, and occurrence of adverse events:

	EORA n (%)	YORA n (%)	p
Corticosteroids average time of Consumption (months)	14.7±25.2[0-120]	13.8±23.2[0-120]	0.7
Total cumulative dose of corticosteroids (g)	6.1 ±9.4 [0-40]	4.7±7.7 [0-40]	0.2
Average daily intake of corti-costeroids (mg/day)	5.4±4.5 [0-10]	6.1±4.6 [0-10]	0.2
CsDMARDS	45 (76)	126 (76.2)	0.7
MTX in monotherapy	23 (38.9%)	69 (41.8%)	0.7
MTX+ Sulfasalazine	12 (20,3%)	43 (26%)	0,3
MTX+Hydroxychloroquine	8 (13,5%)	13 (7,8%)	0,1
Leflunomide	2 (3,3%)	1 (0,6%)	0,1
Biotherapy+MTX	0 (0)	14 (8.4)	0.02
Biotherapy	7 (11.8)	17 (10.3)	0.7
Adverse events	8 (13.5)	5 (3)	<0.01
functional rehabilitation (%)	6.7	16.9	0.05
Surgery (%)	6.7	5.4	0.52

EORA : Elderly onset rhumatoïd arthritis, **YORA** : Yong onset rhumatoïd arthritis, **CsDMARDS**: conventional disease-modifying antirheumatic drug, **MTX**: Methotrexate

Specificities of late-onset RA independently of the disease progression's duration and determination of the adjusted odds ratios (Oda)

In our study, the duration of the disease in the EORA group was 3.08±2.96 years versus 8.23±8.03 years in the YORA group, with a significant difference (p<0.001). An adjustment for this factor was made. This is summarized in table IV.

Indeed, the elevation of the HAQ score in people over 65

Table 4. The parameters adjusted to the duration of the disease.

		EORA N(%)	YORA N(%)	P	Gross odds ratio IC95%	Adjustment to the disease's progression(ORa)	p
Comorbidities	no	21 *(35.6)*	139 *(84.25)*	**<0,001**	**9.6 [4.9-19]**	**8.4 [4.1-17.1]**	**<0.001**
	yes	38 *(64.4)*	26 *(15.75)*				
General symptoms	good general state	45 *(76.3)*	146 *(88.5)*	**<0.05**	**2.3 [1.1-5.1]**	**2.4 [1-5.5]**	**<0.05**
	deterioration of general condition	14 *(23.7)*	19 *(11.5)*				
Mode of onset	progressive	46 *(77.9)*	156 *(94.6)*	**<0.001**	**4.8 [1.9-12.1]**	**5.10 [1.8-14]**	**<0.01**
	Abrupt	13 *(22.1)*	9 *(5.4)*				
Initial joint involovment	Polyarticular	48 *(81.4)*	153*(92.7)*	**<0.05**	**2.9 [1.2-7]**	**3.3 [1.3-8.2]**	**<0.01**
	Oligoarticular	11 *(18.6)*	12 *(7.3)*				
Initial articular presentation	Accromelic	50 *(84.8)*	159 *(97.4)*	**<0.01**	**4.7 [1.6-14]**	**4.8 [1.5-15.6]**	**<0.01**
	Rhizomelic	9 *(15.2)*	6 *(3.6)*				
GPA : global pathology assessment	<70	42 *(71.1)*	162 *(98.1)*	**<0.001**	**21.8 [6.1-7]**	**17.1 [4.4-65.4]**	**<0.001**
	≥70	17*(28.9)*	3*(1.9)*				
HAQ: health assessment	<2	16 *(27.1)*	122 *(74)*	**<0.001**	**7.6 [3.8-14.9]**	**6.8 [3.4-13.6]**	**<0.001**
questionnaire	≥2	43*(72.9)*	43 *(26)*				
Osteoporosis		26 *(44)*	32 *(19.3)*	**<0.001**	**3.2 [1.7-6.2]**	**4.4 [2.1-9.3]**	**<0.001**
Use of Methotrexate		43 (72.8)	139 (84.2)	**0.055**	1.9 [0.9-4]	2 [0.9-4.6]	0.12
Functional rehabilitation		4 *(6.7)*	28 *(16.9)*	0.055	2.8 [0.94-8.38]	**4.5 [1.3-15.8]**	**0.02**
Adverse events	yes	8 *(13.5)*	5 *(3)*	**<0.01**	**5 [1.5-16]**	**4.7 [1.3-16.4]**	**<0.05**
	no	51 *(86.5)*	160 *(97)*				

EORA: Elderly on set Rheumatoid arthritis, **YORA**: young onset rheumatoid arthritis, **P**: p-value obtained by t-test and chi-square test

Discussion

Our study showed that comorbidities were significantly more frequent in the EORA group (ORa=8.4 CI=4.17-17.1; p<0.01), and osteoporosis was also significantly more frequent in this group (ORa=4.4 CI=2.1-9.3; p<0.001). General signs at the initial clinical presentation of the disease were significantly more frequent in the EORA group (ORa=2.4 CI=1-5.5; p<0.05). The onset of RA in both groups was predominantly progressive and polyarticular. However, in the EORA group, rhizomelic involvement and abrupt onset were significantly more frequent than in the YORA group, with respectively (ORa=4.8 CI=1.5-15.6; p<0.01) and (ORa=5.1 CI=1.8-14; p<0.01). GPA was significantly greater in the EORA group (ORa=17.15 CI= 4.49-65.46; p<0.001). The HAQ score was significantly higher in the EORA group, reflecting a greater impact of the disease (ORa=6.8 CI=3.4-13.6; p<0.001). Therapeutic prescriptions were comparable except for the YORA group, which had a significantly higher prescription rate (p<0.001). Adverse events were more frequently found in the EORA group (ORa=4.7 CI=1.3-16.4, p<0.05).

Clinical features

The onset of RA in both groups was readily progressive and polyarticular. However, in the EORA group, we noted a rhizomelic involvement and an abrupt onset significantly more frequent than in the YORA group. This has been consistently demonstrated and several studies have shown that this clinical form is associated with a better prognosis.(2) The causes are not yet well understood, although some theories suggested, in the past, that what is diagnosed as Elderly onset RA can actually be polymyalgia rheumatica,(9) the opposite has also been reported,(10) however, our results do not support this hypothesis.

In our study, disease duration in the YORA group was significantly greater. This was a confounding factor in the comparison between the EORA and YORA groups which led us to make an adjustment for this factor.

Chiu Y et al conducted a Chinese cross-sectional study including 457 patients matched on demographic characteristics. The authors concluded that longer disease duration was associated with higher DAS28 and HAQ scores.(11) Aletaha et al. noted in their study that the longer the duration of the disease, the higher the HAQ score.(12) Treharne G et al. concluded from a cohort of 348 patients that the duration of the disease was associated with the frequency of comorbidities, which subsequently influenced the therapeutic strategy.(13)

Cho SK and colleagues also showed that disease duration ≥ 10 years as well as older age(≥40 years) were associated with higher functional impairment, but onset age was not.(14)

Hence, disease duration could have a greater impact on the course of the disease than advanced age itself.

The impact of RA on quality of life was greater in the EORA group compared to the YORA group, in the present study, despite a shorter disease duration.

years of age has been confirmed in several studies and in particular in those over 75 years of age (1). This score tended to improve less in these patients, even under treatment,(15) which is explained by the impact of the consequences of aging itself on this functional score. Thus, it is sometimes difficult to distinguish the age-related part from the RA-related part in the HAQ score.

Osteoporosis and comorbidities

The bone impact of RA encompasses periarticular bone demineralization, bone erosions, and osteoporosis.(2) Osteoporosis was about four times more frequent in the EORA group. Several factors seem to be involved in the occurrence of osteoporosis in this group of patients, including age, which is the main confounding factor in this case,(16) menopause, decreased physical activity, eating, digestion, and dental disorders that may be the consequence of a low calcium and vitamin D diet, and smoking. Osteoporosis in late-onset RA also includes disease-related factors such as disease activity, chronic disease inflammation, structural damage and joint deformity, and the duration of disease progression. (2) Other risk factors have been identified such as corticosteroid use, rheumatoid factor positivity, and decreased physical activity due to age and functional disability.(2)

Comorbidities were eight times more frequent in the EORA group, mainly cardiovascular diseases, and diabetes. These were more related to the age of the patients than to the age of onset of RA. This aligns with the literature.(17)

Comorbidities have an impact on the autonomy and functional capacity of patients, the frequency of hospitalization, medical costs, and mortality, and they strongly condition the choice of treatments.(18) On the other hand, several studies have shown that aging and comorbidities can independently modify RA assessment parameters, including functional impact, quality of life, radiological scores, response to treatments, and the probability of achieving remission.(19)

Cardiovascular diseases are the most frequent comorbidities and the most common cause of death in patients with RA.(17) And although some papers have shown that practitioners tend to adopt a less aggressive strategy in treating EORA patients,(5,20) other reports have pointed out the role of DMARDs in reducing the risk of CV events in patients with inflammatory arthritis by limiting inflammation and controlling the disease activity. (21)

Hence, treat to target strategies in EORA patients should be better appraised in order to draw solid and concrete conclusions.

Therapeutic distinctions and adverse events

Regarding the therapeutic strategy, it is important to consider the pharmacokinetic parameters of the administered drugs such as absorption, distribution, metabolism, and elimination in the elderly. Furthermore, holistic management requires multidisciplinary therapeutic management, including drug, surgical, physical, dietary, psychological, educational, social, and professional interventions.

In our study, the prescription of analgesics was comparable between the two groups without a significant difference ($p=0.2$), while the prescription of anti-inflammatory drugs was significantly higher in the YORA group ($p<0.001$). EORA patients are especially at risk since RA alone increases the risk of cardiovascular events, to which is added the risk of aging. A recent Danish review on the cardiovascular effects and safety of NSAIDs underlined the adverse effects of these molecules, especially in the older population.(22)

In our study, there were no adverse events following corticosteroid use in either group. However, the role of corticosteroids in the management of RA remains controversial. Their symptomatic effect, in the short term on disease activity, and in the medium term on structural progression, is outweighed by their metabolic and bone-related adverse effects.(7) Additionally, corticosteroid doses taken even up to 2.5 years ago were associated with an increased current risk of serious infection in older patients with RA.(23)

Methotrexate was the most frequently prescribed cs DMARD in both groups, mainly in monotherapy. All current recommendations place MTX as an anchor drug, which should be started as soon as possible after the diagnosis of RA. Indeed, in the absence of contraindications, MTX should be the first choice and should be started at a low dose (10-15mg/week).(2) In fact, it has shown its overall efficacy among the elderly (6) and, according to some studies, EORA patients are more frequently prescribed MTX monotherapy than younger patients.(24,25)

In addition to that, due to the age-related modifications in pharmacokinetics in the elderly, MTX is often prescribed at a lower dose in EORA patients compared to YORA patients.(24)

MTX was also reported to have a better GI tolerance compared to other CsDMARDS, mainly sulfasalazine in older patients.(24)

Furthermore, the potential beneficial effect of MTX on lipoprotein function and cholesterol metabolism could prompt us to use this drug in EORA patients.(2)

Contrariwise, studies of leflunomide in the elderly are limited? In our study, leflunomide was well tolerated. Leflunomide is a DMARD with similar efficacy to MTX in RA. It can be used as an alternative in patients who do not tolerate or have an incomplete response to MTX.(24)

Hydroxychloroquine (HCQ) and sulfasalazine (SSZ) can be used as monotherapy in mild, slowly progressive RA in the elderly. They could be better tolerated and may be preferred in elderly patients with other comorbidities. HCQ was even associated with a lower risk of developing chronic kidney disease in RA patients, regardless of age. (24)

The most prescribed b-DMARD in the EORA group in our study was etanercept, following studies in the literature.(2) Using MTX and biotherapy combination was significantly lower in EORA patients in our study compared to YORA patients. This has been reported in several studies.(24)

When used in combination, MTX acts synergistically to improve the clinical efficacy of monoclonal antibodies, including infliximab and adalimumab, by reducing the immunogenicity of these agents and increasing their serum concentration in blood.

Due to its short half-life, ETN is often preferred in older patients. ETN was also well tolerated regardless of age. (24)

Similarly, other TNF inhibitors have proven their overall safety and efficacy in RA patients of all ages, although data on the efficacy of tocilizumab, rituximab, and tofacitinib in RA in the elderly are limited.

On the other hand, evidence about the good tolerance, efficacy, and safety of Abatacept in the Elderly is available in the literature.(2) But, in our study, none of the patients received this molecule.

Interestingly, despite the clue available in the literature, elderly RA patients still linger to receive optimal treatment, sometimes in spite of high disease activity. (26)

Regarding this matter, Annemieke et al published an interesting review on aging and its influence on the management of RA (27) and suggested a tailored therapy in which disease activity and severity, risk factors for adverse effects of drugs, comorbidities, and the patient's biological, rather than chronological age, are important mainstays. Lina S et al also suggested a similar clinical approach in which the treat-to-target strategy was adopted first in low-risk elderly RA patients (according to the presence or absence of comorbidity, polypharmacy, and cognitive dysfunction).(2)

Concerning adverse events, their occurrence under treatment was almost five times more frequent in the EORA group compared to the YORA group. Polymedication constitutes a hurdle when deciding to treat EORA patients. Comorbidities, particularly cardiovascular diseases, diabetes, and altered renal function participate in declining the tolerance for DMARDS. Based on the findings of European biologic registries and the German biologic registry, comorbidities were predictors of adverse events at the start of b-DMARDS.(28) The risk of infection is one of the most serious adverse events due to the decline of the immune system over the years. A randomized controlled clinical study of Etanercept in the US showed slightly increased adverse events such as serious infections and cancer but concluded that etanercept improved significantly the disease activity and function without however inducing additional safety concerns in EORA patients.(29) A French cohort study, published in 2014, pointed out the decreased efficacy and safety of Rituximab in the elderly with an increased DAS-28 score after the sixth month, and increased risk of infections.(30) Caution and assessment of the benefit-risk equation when treating EORA patients should, therefore, always be suggested.

As RA must benefit from multidisciplinary management, rehabilitation, in our study, was advocated in 6.7% of the EORA group versus 16.9% of the YORA group, with a significant difference, (ORa=4.73 [1.36-16.47), p=0.02). The main objectives of physical treatment are pain reduction, prevention or treatment of deformities, maintenance or recovery of joint mobility and stability, maintenance of muscle performance and aerobic capacity and physical coordination, functional adaptation, and prevention of disability.(31) Physical therapy remains a cornerstone in the management of RA. Indeed, various studies have provided a strong rationale for the importance of a sustainable increase in physical activity in patients with RA.(31) Likewise, a recent systemic literature review on difficult-to-treat RA patients found that non-pharmacological interventions, including exercise, improved non-inflammatory complaints mainly functional disability, pain, and fatigue.(32)

Exercise therapy is recommended at the rate of 3-5 days/ week for 30-60 min/ session combining both aerobic exercise and muscle strengthening, which can be delicate for the elderly.(33) Various therapies are recommended depending on the disease activity, and specific targets should be consistently stated.(33,34)

Surgical treatment in the EORA group was performed in 6.7% of the patients versus 5.4% in the YORA group with p=0.52. Joint replacement in RA is mainly performed in the elderly, with total hip or knee replacement being the most common surgical procedure. This aligns with the literature findings.(35) It is indicated in cases of advanced joint damage with significant functional repercussions. The advances in the pharmacological treatment of RA have revolutionized the management of the disease, thus, contributing to lower rates of joint surgery.(35,36)

Highlights and limitations

The sample studied was representative of the patients consulting our institute, which is a specialized center in musculoskeletal pathology, and their number was sufficient to have statistically reliable results.

Our case-control study allowed the identification of clinical, immunological, radiological, and therapeutic specificities of RA starting after the age of 65 years. Nevertheless, it had some limitations. In fact, this was a single-center, cross-sectional study that did not allow the assessment of the long-term evolution of the disease.

Conclusion

Compared to younger-onset RA, elderly-onset RA (EORA) shows a more balanced gender ratio and distinct clinical patterns like acute oligoarthritis and worse general condition. Comorbidities and osteoporosis are more common, with no unique biological, radiographic or therapeutic markers. Despite age, EORA patients should receive targeted, optimal treatment aiming for remission, considering comorbid risks and overall health. Age alone shouldn't limit care intensity.

References

1. Acuña-Rocha VD, Regalado-Ceballos D, Salcedo-Soto DA, Ramos-Delgado CA, Esquivel-Valerio JA, Hernandez Galarza IJ, et al. Clinical Characteristics of Young-Onset Versus Elderly-Onset Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Cureus. 2024 Nov;16(11):e74148.
2. Serhal L, Lwin MN, Holroyd C, Edwards CJ. Rheumatoid arthritis in the elderly: Characteristics and treatment considerations. Autoimmun Rev. 2020 Jun;19(6):102528.
3. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315–24.
4. Kim HO, Yoon HS, Kwok SK, Ju JH, Park KS, Park SH, et al. Clinical Characteristics of Elderly Onset Rheumatoid Arthritis. J Korean Geriatr Soc. 2010 Dec 1;14(4):227–33.
5. Pérez N, Gargiulo M de LÁ, Khoury M, Suárez L, Correa M de LÁ, Pera M, et al. Elderly-onset rheumatoid arthritis receives less aggressive therapies than young-onset rheumatoid arthritis in an Argentinian cohort. Reumatol Clin. 2024 Mar;20(3):136–41.
6. Sugihara T, Ishizaki T, Onoguchi W, Baba H, Matsumoto T, Iga S, et al. Effectiveness and safety of treat-to-target strategy in elderly-onset rheumatoid arthritis: a 3-year prospective observational study. Rheumatol Oxf Engl. 2021 Sep 1;60(9):4252–61.
7. Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis. 2015 Feb 1;74(2):415–21.
8. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatol Oxf Engl. 2012 Dec;51 Suppl 6:vi5-9.
9. Wilkieson CA, Madhok R, Hunter JA, Capell HA. Toleration, side-effects and efficacy of sulphasalazine in rheumatoid arthritis patients of different ages. Q J Med. 1993 Aug;86(8):501–5.
10. Kermani TA, Warrington KJ. Polymyalgia rheumatica. Lancet Lond Engl. 2013 Jan 5;381(9860):63–72.
11. Chiu YM, Lai MS, Lin HY, Lang HC, Lee LJH, Wang JD. Disease activity affects all domains of quality of life in patients with rheumatoid arthritis and is modified by disease duration. Clin Exp Rheumatol. 2014 Dec;32(6):898–903.
12. Aletaha D. Duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. Ann Rheum Dis. 2006 Feb;65(2):227–33.
13. Treharne GJ, Douglas KMJ, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care. 2007 Dec;5(4):175–90.
14. Cho SK, Sung YK, Choi CB, Cha HS, Choe JY, Chung WT, et al. Do patients with elderly-onset rheumatoid arthritis have severe functional disability? Semin Arthritis Rheum. 2012 Aug;42(1):23–31.
15. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. Rheumatol Oxf Engl. 1999 Mar;38(3):228–34.
16. Roux C. Osteoporosis in inflammatory joint diseases. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2011 Feb;22(2):421–33.
17. Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-articular manifestations and comorbidities. Autoimmun Rev. 2021 Apr;20(4):102776.
18. Curi YS, Lucero LG, Hüttmann FJ, Leguizamón ML, Mazza SM, Espasa GV, et al. Fri0603-Hpr Comorbidities in Rheumatoid Arthritis: Utility of Raci Score (rheumatoid Arthritis Comorbidity Index). Ann Rheum Dis. 2020 Jun 1;79(Suppl 1):907–8.
19. Kłodziński Ł, Wisłowska M. Comorbidities in rheumatic arthritis. Reumatologia. 2018;56(4):228–33.
20. Salomon-Escoto K, Kay J. The "Treat to Target" Approach to Rheumatoid Arthritis. Rheum Dis Clin North Am. 2019 Nov;45(4):487–504.
21. Lee JL, Sinnathurai P, Buchbinder R, Hill C, Lassere M, March L. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. Arthritis Res Ther. 2018;20:171.
22. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. Nat Rev Cardiol. 2020 Sep;17(9):574–84.
23. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012 Jul;71(7):1128–33.
24. Kumagai K, Okumura N, Amano Y, Yayama T, Mimura T, Maeda T, et al. Consideration of differences in drug usage between young-onset and elderly-onset rheumatoid arthritis with target of low disease activity. Mod Rheumatol. 2021 Nov;31(6):1094–9.
25. Takanashi S, Kaneko Y. Unmet Needs and Current Challenges of Rheumatoid Arthritis: Difficult-to-Treat Rheumatoid Arthritis and Late-Onset Rheumatoid Arthritis. J Clin Med. 2024 Dec 13;13(24):7594.
26. Baimukhamedov Ch. Elderly-onset rheumatoid arthritis: an outlook from a practicing rheumatologist. Rheumatol Sci Pract. 2020 Sep 4;58(4):447–50.
27. Boots AMH, Maier AB, Stinissen P, Masson P, Lories RJ, De Keyser F. The influence of ageing on the development and management of rheumatoid arthritis. Nat Rev Rheumatol. 2013 Oct;9(10):604–13.
28. Kearsley-Fleet L, Zavada J, Hetland ML, Nordstrom DC, Aaltonen KJ, Listing J, et al. The EULAR Study Group for Registers and Observational Drug Studies: comparability of the patient case mix in the European biologic disease modifying anti-rheumatic drug registers. Rheumatology. 2015 Jun 1;54(6):1074–9.
29. Bathon JM, Fleischmann RM, Van der Heijde D, Tesser JR, Peloso PM, Chon Y, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):234–43.
30. Payet S, Soubrier M, Perrodeau E, Bardin T, Cantagrel A, Combe B, et al. Efficacy and safety of rituximab in elderly patients with rheumatoid arthritis enrolled in a French Society of Rheumatology registry. Arthritis Care Res. 2014 Sep;66(9):1289–95.
31. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. Best Pract Res Clin Rheumatol. 2018 Oct;32(5):669–82.
32. Roodenrijs NMT, Hamar A, Kedves M, Nagy G, van Laar JM, van der Heijde D, et al. Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. RMD Open. 2021 Jan;7(1):e001512.
33. Küçükdeveci AA. Nonpharmacological treatment in established rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2019 Oct;33(5):101482.
34. Ben Tekaya A, Rouached L, Ben Dhia S, Bouden S, Tekaya R, Mahmoud I, et al. Physical activity assessment in rheumatoid arthritis: a 120-patient cross-sectional study. Tunis Med. 2024 Jun 5;102(6):348–53.
35. Nikiphorou E, Konan S, MacGregor AJ, Haddad FS, Young A. The surgical treatment of rheumatoid arthritis: a new era? Bone Jt J. 2014 Oct;96-B(10):1287–9.
36. Zhou VY, Lacaille D, Lu N, Kopec JA, Garbuz DS, Qian Y, et al. Has the incidence of total joint arthroplasty in rheumatoid arthritis decreased in the era of biologics use? A population-based cohort study. Rheumatol Oxf Engl. 2022 May 5;61(5):1819–30.