LATE ONSET RHEUMATOID ARTHRITIS: AN OBSERVATIONAL STUDY

REUMATOIDNI ARTRITIS KASNOG NASTUPA: OPSERVACIJSKA STUDIJA

Sylejman Rexhepi[1], Mjellma Rexhepi[1], Vjollca Sahatçiu-Meka[2], Blerta Rexhepi[1], Elton Bahtiri[3], Vigan Mahmutaj[1]

[1] Clinic of Rheumatology, University Clinical Centre of Kosovo, Rr. "Bulevardi i Dëshmorëve", 10000 Prishtina, Kosovo
[2] Faculty of Medicine, University of Prishtina, Rr. "Bulevardi i Dëshmorëve", 10000 Prishtina, Kosovo
[3] Faculty of Medicine, University of Prishtina, Rr. "Bulevardi i Dëshmorëve", 10000 Prishtina, Kosovo

Corresponding author:
Blerta Rexhepi
Clinic of Rheumatology, University Clinical Centre of Kosovo
Rr. "Mehmet Gradica"
Lamela 11/9
10000, Prishtina
Kosovo
Mob: +377 44 234 156
E-mail: blerta.rexhepi@gmail.com

Abstract. Rheumatoid arthritis (RA) may have an onset at older age. The onset of the disease at the age of 60 and over is called late-onset rheumatoid arthritis (LORA). The aim of this study was to analyze the clinical, laboratory, radiological, and treatment characteristics of patients with LORA compared to those with early-onset RA (EaORA), provided that all the patients had an approximately equal duration of the disease. This is an observational single-center study, which involved 120 patients with an established diagnosis of RA, of which 60 patients had LORA, and 60 patients EaORA. The disease activity, measured by the Disease Activity Score 28 (DAS28-ESR), was significantly higher in the LORA group compared to the EaORA group (p<0.05). Significantly more patients with LORA had involvement of the shoulders (LORA vs. EaORA, 30% vs. 15%; p <0.05) and knees (LORA vs. EaORA, 46.7% vs. 16.7%; p <0.05). Radiological erosive changes were significantly more frequent in the LORA group in comparison with EaORA (p <0.05). There was no difference between the groups regarding rheumatoid factor (RF) positivity (p>0.05), while the number of patients positive for anti-citrullinated protein antibody (ACPA) was significantly greater in the EaORA group (p<0.05). The values of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were significantly higher in the LORA than in the EaORA group. Hemoglobin levels were lower in the LORA group (11.96±1.64 g/dL) than in the EaORA group (12.18±1.56 g/dL). The most used disease-modifying antirheumatic drugs (DMARDs) were methotrexate and sulfasalazine, while biological drugs were not used.

In conclusion, based on the results of our study, LORA has some features that distinguish it from EaORA, such as higher disease activity, more frequent involvement of large joints, and more pronounced structural damage. This should be taken in account in clinical practice, especially regarding treatment choices.

Sažetak. Reumatoidni artritis (RA) može imati početak u starijoj životnoj dobi. Nastup bolesti sa 60 i više godina naziva se RA kasnog početka (engl. *Late-Onset Rheumatoid Arthritis* – LORA). Cilj ove studije bio je analizira-

Professional paper

Rexhepi S. et al. Late onset rheumatoid arthritis: an observational study

ti klinička, laboratorijska, radiološka obilježja i obilježja liječenja u bolesnika s LORA-om u usporedbi s RA ranijeg početka (engl. *Early-Onset Rheumatoid Arthritis* – EaORA) s tim da su pacijenti u obje grupe bili približno jednakog trajanja bolesti. Radi se o opservacijskoj studiji provedenoj u jednome reumatološkom centru, koja je uključila 120 bolesnika s utvrđenom dijagnozom RA podijeljenih u dvije grupe: 60 bolesnika s LORA-om (istraživana grupa) i 60 bolesnika s EaORA-om (kontrolna skupina). Aktivnost bolesti, mjerena *Disease Activity Score 28* (DAS28SE) bila je značajno viša u grupi LORA u odnosu prema grupi EaORA (p < 0,05). Značajno više bolesnika u grupi LORA imalo je zahvaćena ramena (LORA vs. EaORA, 30% vs. 15%; p < 0,05) i koljena (LORA vs. EaORA, 46,7% vs. 16,7%; p < 0,05). Radiološke erozivne promjene bile su značajno češće vidljive u grupi LORA u usporedbi s grupom EaORA (p < 0,05). Nije bilo razlike među grupama glede reumatoidnog faktora (RF) (p > 0,05), dok je broj pacijenata s pozitivnim nalazom anticitulinirajućih protutijela (ACPA) bio značajno veći u grupi EaORA (p < 0,05). Vrijednosti C-reaktivnog proteina (CRP) i brzina sedimentacije eritrocita (SE) bile su značajno više/brže u grupi LORA u odnosu prema grupi EaORA. Hemoglobin je bio niži u grupi LORA (11,96 ± 1,64 g/dl) nego u grupi EaORA (12,18 ± 1,56 g/dl). Najčešće primijenjeni lijekovi koji mijenjaju tijek upalnih reumatskih bolesti bili su metotreksat i sulfasalazin, dok biološki lijekovi nisu bili upotrijebljeni.

U zaključku, na temelju rezultata iz našeg istraživanja, bolesnici s LORA-om imaju neka obilježja koja se razlikuju od onih u bolesnika s EaORA-om, kao što su viša aktivnost bolesti, češća zahvaćenost velikih zglobova i veće strukturne promjene. Ovo se mora uzeti u obzir u kliničkom radu, napose u odabiru terapije.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, leading to reduced physical function and impaired quality of life. The onset of the disease at the age of 60 and over is often labeled as late-onset rheumatoid arthritis (LORA).[1] From the total number of patients with RA, LORA accounts for 10 % to 33% of patients, and the gender ratio is equal for both sexes. The symptoms of LORA differ from common forms of RA, with more common diffuse swelling of the palms, localization in large joints, and diffuse osteoporosis.[2] In most cases, it is associated with severe onset, involvement of large joints (predominantly shoulders), as well as a prompt increase of inflammatory reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[3] Positive rheumatoid factor (RF) and extra-articular manifestations, including subcutaneous nodes, are generally less frequent than in RA.[4] Other rheumatic diseases, such as spondyloarthritides, psoriatic arthritis, and polymyalgia rheumatica may also begin at an older age and thus have to be considered in the differential diagnosis. In some studies, authors have reported that patients with LORA have a milder form of the disease than those with early-onset RA (EaORA).[5] Nevertheless, other unfavorable factors can reduce function early in the disease. LORA patients with a positive RF have the worst performance in terms of disease morbidity and mortality. Positive anti-citrullinated protein antibody (ACPA) was reported in up to 56–65% patients with LORA. It should be emphasized that the increase of ACPA in LORA patients has been associated with radiological damage. Regarding the treatment, patients with LORA are usually treated in the same way as patients with EaORA. The main difference in comparison with polymyalgia rheumatica is the presence of positive ACPA in LORA.[6] Due to earlier erosive changes in LORA, conventional X-ray might be more useful in establishing the diagnosis, although structural changes can be detected at a much earlier time with the use of ultrasound or magnetic resonance.[7] All the above-mentioned facts related to LORA show that this form of RA can be called heterogeneous and has its distinctive features compared to EaORA.

The aim of this study was to compare the clinical, laboratory, and radiological features as well as the treatment options for patients with LORA and EaORA in the everyday clinical setting within the well-defined ethnic Albanian population of Kosovo.

Materials and methods

This was an observational study conducted in 120 patients with an established diagnosis of RA fulfilling the American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) 2010 criteria for RA. The study was carried out at the Clinic of Rheumatology, University Clinical Centre of Kosovo, during a 12-month period (June 2014 to June 2015). All procedures in the study were approved by and performed in accordance with the ethical standards of the local ethics committee, as well as the Helsinki Declaration of 1975, as revised in 1983. A sample of 120 patients with approximately the same duration of the disease of around 5 years was selected, involving 60 patients with LORA (study group) (age at onset ≥ 60 years) and 60 patients with EaORA (control group) (age at onset < 60 years). The structured questionnaire specifically designed for this study included sociodemographic data, clinical, laboratory, and radiological characteristics of the patients, as well treatment options. The patients' disease activity was measured using the Disease Activity Score (DAS-28-ESR), while the Health Assessment Questionnaire – Disability Index (HAQ-DI) was used to assess functional ability. Routine laboratory findings were collected. The normal value of the erythrocyte sedimentation rate (ESR) was defined as ≤ 15mm/h and for C-reactive protein (CRP) it was < 6 mg/L. Positivity for ACPA was defined as >17 IU/ml, and for rheumatoid factor (RF) as >15 IU/

mL. Reference values for hemoglobin were in the range 11.0–18.0 g/dL.

Statistical analysis

Continuous variables are expressed as means ± standard deviations or median and range, while categorical data are presented as number and percentages. Differences in the study variables between groups were compared using t-test or χ^2 test, as appropriate. Statistical analysis was performed using SPSS software version 16.0. A p-value of <0.05 was considered statistically significant.

Results

The average age of the study group (LORA) was 71.75 ± 5.30 years, and in the control group (EaORA) it was 44.85 ± 8.80 years. The duration of the disease in the study group (LORA) was 4.97 ± 2.22 years, and in the control group (EaORA) it was 4.63 ± 4.53 years, with no significant difference between them (p>0.05). In the LORA group there were 48 females and 12 males, while in the EaORA group there were 51 females and 9 males. The disease activity, measured by DAS28-ESR, was significantly higher in the study group (LORA) (5.9±2.0) compared to the control group (EaORA) (3.5±1.5). (p<0.05). There was no difference regarding physical function assessed by HAQ (LORA

group vs. EaORA group, 0.64±1.0 vs. 1.0±1.5) (p>0.05). Regarding large joint involvement, shoulder joints were affected more frequently in the study group (LORA) (18 subjects; 30%) compared to the control group (EaORA) (9 subjects; 15%) (p<0.05). There was a difference in knee involvement (LORA group – 28 subjects; 46.7% vs. EaORA – 10 subjects; 16.7%) (p <0.05), but not in the involvement of the elbows (LORA – 19 subjects; 31.7% vs. EaORA – 17 subjects; 28.3%) (p>0.05). The proximal interphalangeal joints (PIP) were more affected by the disease in the study group (54 subjects; 90%) than in the control group (19 subjects; 31.66%) (p<0.05). Radiological erosive changes were significantly more frequent in the study group of LORA in comparison with the control group of EaORA (54 subjects versus 19 subjects, respectively) (p<0.05). Subcutaneous nodes were found in 3 subjects (5%) in the study group (LORA) compared to 5 subjects (8.3%) in the control group (EaORA) (Table 1).

Regarding RF positivity, there were no differences between the two groups (LORA vs. EaORA – 40 vs. 40 subjects, p>0.05), while the number of patients positive for ACPA was significantly greater in the control group (EaORA) compared with the study group (LORA) (56 subjects vs. 15 subjects, respectively) (p <0.05). The CRP level was significantly higher in the study group (LORA) (49.94±34.72 mg/L) compared with the control group

TABLE 1 Clinical and radiological characteristics of study subjects
TABLICA 1. Kliničke i radiološke karakteristike ispitanika uključenih u istraživanje

	Study group (LORA) (n=60)		Control group (EaORA) (n=60)		P value
Mean age (yrs.)	71.75±5.30		44.85±8.80		p<0.05
Average duration of disease (yrs.)	4.97±2.22		4.63±4.53		p<0.05
Localization in large joints	N	%	N	%	
Shoulder	18	30	9	15	p<0.05
Elbow	19	31.7	17	28.3	p>0.05
Knee	28	46.7	10	16.7	p<0.05
Hand joints (PIP, MCP)	54	90	21	35	p<0.05
Radiological erosive changes	54	90	19	31.66	p <0.05
Subcutaneous nodes	3	5	5	8.3	p>0.05

PIP – proximal interphalangeal, MCP – metacarpophalangeal

TABLE 2 Laboratory findings of study subjects
TABLICA 2. Laboratorijska obilježja ispitanika uključenih u istraživanje

	Study group (LORA) (n=60)		Control group (EaORA) (n=60)		P value
	N	%	N	%	
Patients positive for RF*	40	66.6	40	66.6	p>0.05
Patients positive for ACPA**	15	25	56	93.3	p<0.05
C-Reactive Protein (mg/dL)	49.94±34.72		27.75±36.16		p<0.05
Erythrocyte Sedimentation Rate (mm/h)	58.95±30.45		34.52±23.48		p<0.05
Hemoglobin (g/L)	11.96±1.64		12.18±1.56		p>0.05

 * *Rheumatoid factor (RF)*
** *Anti-citrullinated protein antibody (ACPA)*

Professional paper

Rexhepi S. et al. Late onset rheumatoid arthritis: an observational study

TABLE 3 Drugs used for treatment of study subjects

TABLICA 3. Lijekovi primijenjeni u liječenju bolesnika uključenih u studiju

	Study group (LORA) (n=60)		Control group (EaORA) (n=60)		P value
	N	%	N	%	
NSAIDs	2	3.3	2	3.3	p>0.05
Glucocorticoids	0		3	5	p<0.05
NSAIDs* and Glucocorticoids	53	88.3	54	90	p>0.05
DMARDs**					
Methotrexate	49	81.7	50	83.3	p>0.05
Sulfasalazine	28	46.7	14	23.3	p<0.05
Hydroxychlorochine	8	13.3	2	3.3	p<0.05

 * *NSAIDs – nonsteroidal anti-inflammatory drugs*
** *DMARDs – disease-modifying antirheumatic drugs*

(EaORA) (27.75±36.16 mg/L). Also, the ESR value was higher in the study group (LORA) (58.95±30.45 mm/h) compared to the control group (EaORA) (34.52±23.48 mm/h). There was no difference in regard to hemoglobin values (LORA vs. EaORA – 11.96±1.64 g/L vs. 12.18±1.56 g/L respectively) (Table 2).

Regarding treatment choices in both groups, the most used DMARDs were methotrexate and sulfasalazine, with some, but not consistent, differences between the groups (Table 3). Biological substances were not included in the treatment because of the high cost of these drugs.

Discussion

The objective of this study was to explore the differences in the clinical, laboratory, radiological, and treatment characteristics of patients with LORA in comparison to those with EaORA. It is known that RA has its peak incidence in young and middle-aged adults and that its later onset has some distinctive features.[8] In our study of ethnic Albanian residents of Kosovo it was confirmed that patients with LORA have greater functional impairment, higher disease activity, and more radiographic damage at the same duration of the disease compared to those with EaORA. These results are in accordance with other similar studies. In the study conducted by Turcapar et al. the male-female gender ratio in LORA patients was 1.3:1, i.e., without the striking female preponderance seen in EaORA.[9] Also, large joint involvement, especially of the shoulder and knee, was significantly higher in LORA patients, like in our study. The EaORA patients in our study were significantly more positive for ACPA compared to LORA patients. Berglin et al. found an association between the radiological damage in RA and the presence of ACPA before or at disease onset.[10] A higher prevalence of positive ACPA was observed in EaORA patients, and a decreased prevalence of ACPA with increasing age at onset of RA.[10] In our research study, the frequency of RF positivity was similar for both groups, which is consistent with previously published studies by van der Heijde et al.[11] The presence of radiological erosions found in our

LORA group of patients is in accordance with other studies, which found a tendency towards more radiographically detected damage in older patients compared to those younger than 60 years.[11] Furthermore, Bukhari et al. showed that an older age at the onset of symptoms was associated with an increased occurrence of erosions during the first 12 months in patients diagnosed with early polyarthritis.[12] Our study results also showed that a significantly higher HAQ score at baseline was associated with LORA. This finding is similar to that reported by Pease et al., who found that patients over 65 years had a higher HAQ score at baseline (results derived from the Norfolk Arthritis Register).[13] Overall, it can be stated that patients with LORA have a greater level of disability and higher functional impairment compared to those with EaORA.[14] It is of crucial importance to highlight that lately the focus of rheumatologists has been on the diagnosis and treatment of early-onset RA, in order to prevent erosion. Considering that, LORA differs from EaORA in some important ways. It has been proven to be somewhat difficult to diagnose LORA because of its clinical features overlapping with some other rheumatic diseases, such as polymyalgia rheumatica. Apart from the similar clinical features, both diseases present with similar laboratory findings that include higher CRP and accelerated ESR along with anemia. As for the radiological level of damage, we confirmed previous findings of it being more pronounced in LORA than in EaORA.[15–17] In our study, the pharmacological treatment was different between the groups regarding the use of glucocorticoids (more patients in the EaORA group) or sulfasalazine and hydrohyclorochine (more patients in the LORA group). The challenge of treating patients with LORA is polypharmacy, as a consequence of comorbidities. In our opinion, more aggressive treatment for patients with LORA should be used. There were no significant adverse events, such as gastrointestinal disturbances, stomatitis, alopecia, or liver abnormalities, all of which can be present in patients treated with DMARDs, especially methotrexate.[18–21]

The main strength of our study is that we based our findings on two defined groups of patients with RA

(LORA and EaORA) of almost the same duration of the disease. There are several limitations of our study, the major one being the observational cross-sectional study design, which has limitations per se.

Conclusion

In our sample of patients with RA it was shown that patients with LORA have some distinct features in comparison to those with EaORA, the most striking ones being a higher disease activity, more frequent involvement of large joints, and more structural damage. Patients with LORA should be recognized and treated more aggressively, taking into consideration existing comorbidities. More longitudinal studies would further elucidate the course of LORA and the optimal treatment approach.

DECLARATION ON CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

REFERENCES

1. Olivieri I, Pipitone N, D'Angelo S, Padula A, Salvarani C. Late--onset rheumatoid arthritis and late-onset spondylarthritis. Clin Exp Rheumatol. 2009 Jul-Aug; 27(4 Suppl 55):S139–45.

2. Rexhepi S. Reumatologjia. Prishtina. Twins. 2006.

3. Ehrlich GE, Katz WA, Cohen SH. Rheumatoid arthritis in aged. Geriatrics. 1970;25:103–13.

4. Van Schaardenburg D. Breedveld FC. Elderly onset rheumatoid arthritis. Semin Arthritis Rheum. 1994;23:367–78.

5. Terkeltaub R, Esdaile J, Decary F, Tannenbaum H. A clinical study of older age rheumatoid arthritis with comparison to younger onset group. J Rheumatol. 1983;10:418–24.

6. Lopez-Hoyos M, Ruiz De Alegria C, Blanco R et al. Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Rheumatology (Oxford) 2004;43:655–7.

7. Parodi M, Garlaschi G, Silvestri E, Cimmino MA. Magnetic resonance imaging in the differential diagnosis between polymyalgia rheumatica and elderly onset rheumatoid arthritis. Clin Rheumatol 2006;25:402–3.

8. Villa-Blanco JI, Calvo-Alén J. Elderly onset rheumatoid arthritis: differential diagnosis and choice of first-line and subsequent therapy. Drugs Aging 2009;26:739–50.

9. Turcapar N, Demir O, Atli T i sur. Late onset rheumatoid arthritis: clinical and laboratory comparisons with younger Gerontology Geriatric. 2006;42:225–31.

10. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, Rantapää-Dahlqvist S. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset. Ann Rheum Dis 2006,65:453–458.

11. Van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective followup study of early rheumatoid arthritis. J Rheumatol 1991,18:1285–1289.

12. Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis. Ann Rheum Dis 2007,66:389–393.

13. Camacho EM, Verstappen SM, Lunt M, Bunn DK, Symmons DP. Influence of age and sex on functional outcome over time in a cohort of patients with recent-onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Care Res (Hoboken) 2011;63:1745–52. doi: 10.1002/acr.20609.

14. 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. Rheumatology (Oxford) 1999,38:228–234.

15. Goğüş F.Yaşlı başlangıçlı romatoid artrit: Klinik özellikleri ve ayırıcı tanısı. Turkish Journal of Geriatrics 2005;8:153–7.

16. El-Labban AS, Omar HA, El-Shereif RR, Ali F, El-Mansoury TM. Pattern of young and old onset rheumatoid arthritis (YORA and EORA) among a group of egyptian patients with rheumatoid arthritis. Clin Med Insights Arthritis Musculoskelet Disord 2010;3:25–31.

17. Calvo-Alén J, Corrales A, Sánchez-Andrada S, Fernández--Echevarría MA, Peña JL, Rodríguez-Valverde V. Outcome of late-onset rheumatoid arthritis. Clin Rheumatol 2005;24: 485–9.

18. Bernatsky S, Ehrmann Feldman D. Discontinuation of methotrexate therapy in older patients with newly diagnosed rheumatoid arthritis: analysis of administrative health databases in Québec, Canada. Drugs Aging 2008;25:879–84.

19. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964–975.

20. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008;26:S35–S61.

21. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev. 2005 Jun;57(2): 163–72.