Original Article
DOI: https://doi.org/10.70749/ijbr.v3i5.1205

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Comparison of Time to Remission in Treatment Regimen at Remission between Late Onset Rheumatoid Arthritis (LORA) and Early Onset Rheumatoid Arthritis (EORA) Patient

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ARTICLE INFO

Keywords

Methotrexate, Remission, Rheumatoid Arthritis, Tofacitinib.

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Declaration

Authors' Contribution: All the authors contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 07-02-2025, Revised: 14-04-2025
Accepted: 24-04-2025, Published: 06-05-2025

ABSTRACT

Objectives: To compare the time to remission and treatment regimen at remission between late onset rheumatoid arthritis (LORA) and early onset rheumatoid arthritis (EORA) patients. **Study design:** Prospective cohort study. **Place of duration of study:** Department of Medicine, CMH, Multan from July 2023 to December 2024. **Methods:** A total of 670 patients with an age of onset of active RA ≥ 60 years, diagnosed within 1 year, were included in the LORA group. Other 670 patients with age of onset of active RA between 18-59 years with similar diagnostic details were included in the EORA group. Disease activity was evaluated using the DAS -ESR 28 score. Patients initiated methotrexate (5-15mg/week, maximum 25mg/week). Upon inadequate response to optimal therapy, (DAS28-ESR ≥ 2.6 after 3-6 months), tofacitinib (5mg twice daily) was added to methotrexate or used as monotherapy in intolerant cases, following treat-to-target strategy. The primary outcomes were set as DAS28-ESR scores, proportion of patients achieving remission (DAS28-ESR < 2.6) at 12 months, time to first remission, and treatment regimens at remission. **Results:** The mean age of patients was 68.35±5.99 and 49±5.89 years in group LORA and group EORA respectively. LORA patients were more frequently on methotrexate monotherapy (p=0.04) or methotrexate + tofacitinib combination (0.004) than EORA patients. There was no statistically significant difference in the two groups in DAS28-ESR score achieved and the number of patients achieving DAS28-ESR <2.6 at the completion of study. Comparison of time to remission in patients achieving remission also showed no statistically significant difference among the two groups (p=0.5). **Conclusion:** The remission rate and time to remission remains similar in LORA and EORA patients despite the differences in medication regimens to achieve remission.

INTRODUCTION

Rheumatoid arthritis (RA) is explained as a complex systemic autoimmune disease characterized by progressive inflammation of joints with an extra-articular involvement. The disorder arises with an interplay of genetic predisposition and environmental triggers, initially presenting in smaller peripheral joints in a symmetric pattern, and has potential to progress to larger proximal joints.[1] This inflammatory process, if not timely managed with medical interventions may lead to progressive joint destruction with cartilage degradation and bone erosions causing functional disabilities for the patients over the long term.[2]

The studies conducted over diverse population base and treatment options conclude that the disease progression and clinical outcomes vary among patients depending upon their ages and presenting symptoms.[3] Age at the time of onset serves as crucial determinant in RA progression in shape of disease presentation, progression and treatment response. A key distinction among the RA patients based on their age is, Early-Onset RA (EORA) and Late-Onset RA (LORA), as each one of these has unique disease presentation, progression patterns, and treatment outcome. The definite age range for defining LORA varies in literature, however, most researchers take 60 years as the cutoff age, while the onset before this age will be classified as EORA.[4,5]

The patients with EORA present with higher seropositivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies which lead to more aggressive progression of the disease. In contrast, LORA is characterized by atypical features, such as polymyalgia rheumatica-like symptoms, and may show

lower seropositivity rates. The patients presenting with LORA report with acute onset with predominant large joint involvement and shows prominent constitutional symptoms. There is higher initial disease activity score (DAS) and rapid functional deterioration. LORA is further complicated by increased prevalence of comorbidities, especially the cardiovascular (CV) disease and osteoporosis.[6] EORA patients on the other hand frequently present with gradual onset and predominant small joint involvement.[6,7] This difference in clinical presentation and disease manifestations between EORA and LORA underscores the need for tailored therapeutic strategies to optimize the outcomes. Current treatment guidelines emphasize on early and Intensive treatment aimed at achieving remission or at least low the disease activity, to preclude the joint damage and maintaining the functional capacity of the patients. However, the guidelines do not specifically address this age-related differences in treatment response and not provide distinct recommendations based on age of onset of the disease.[8]

Significant progress has been made in the treatment of RA with the introduction of disease-modifying antirheumatic drugs (DMARDs) during last 2 decades. American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend a conventional synthetic DMARD (csDMARD), methotrexate (MTX), as the first-line treatment in RA. For the patients with inadequate respone, biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), including Janus kinase inhibitors (JAK I), have provided an effective alternative. JAK I have especially demonstrated good efficacy in reducing inflammation and proven to prevent structural damage, specifically in combination to MTX.[9,10]

In the management of RA, achieving clinical remission is mostly evaluated by achieving a DAS28 - ESR < 2.6, which represents as a primary therapeutic goal. Time to remission is also an important and critical metric for evaluating therapeutic efficacy, as a shorter durations is associated with reduced joint damage, and improved quality of life. Earlier research has concentrated on the achievement of DAS28-ESR< 2.6 and time to achieve remission in different subclasses of RA patients, impact of different treatment strategies and different age groups, however, very few have studied the comparison of these parameters between EORA and LORA patients while using standard treat-to-target (T2T) approach.

This study was therefore planned to compare the time to remission and treatment regimen at remission between LORA and EORA patients. The results of this study will help our clinicians to tailor their treatment regimen on the basis of evidence while treating these important sub types of RA.

METHODS

This prospective cohort study was conducted at the Department of Medicine, CMH, Multan from July 2023 to December 2024, over a period of 1.5 years.

Approval of conducting the study was obtained from the ethical committee of the hospital. Sample size of 664 for each group was calculated by using the WHO sample size calculator and keeping the Alpha= 5%, (two sided), power= 80% with p1 (achieved DAS28-ESR score in the LORA group) = 2.5±3.3, while p2 (achieved DAS28-ESR score in the EORA group) = 2±3.2.[11]

Inclusion Criteria: A total of 670 patients with an age of onset of active RA ≥ 60 years (as per defined by ACR and ELAR criteria), diagnosed within last 1 year, were added in the LORA group. Similarly, a total of 670 patients with age of onset of active RA between 18 to 59 years, with the same diagnostic criteria and duration of diagnosis, were included in the EORA group.

Exclusion Criteria: Patients with a history of other autoimmune diseases, with severe comorbidities that could interfere with treatment or inability to attend the planned follow-up visits on regular basis were excluded.

A written informed consent was taken from patients before their inclusion in the study.

A comprehensive baseline assessments was done for all participants including demographic data, disease duration, and onset of symptoms. Details of comorbidities were recorded.

Laboratory evaluations was done to find related serological markers including rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Disease activity was evaluated using the DAS28-ESR**,** Clinical Disease Activity Index (CDAI), and Simple Disease Activity Index (SDAI). A structured follow-up schedule was set which consisted of monthly visits during the first 6 months, followed by visit of quarterly basis until the completion of 12 months.

Treatment regimen followed the protocols set by the ACR/EULAR recommendations.

All the patients were started with a csDMARD (MTX started at 5-15mg/week, optimizing up to 25mg/week if needed and adequate) with regular monitoring of clinical response and adverse events. In case of persistent disease activity despite optimal csDMARD therapy, a T2T strategy was applied (3-6 months of MTX therapy and failure to achieve low disease activity, DAS28 < 2.6, despite optimal dosing and consideration of combination csDMARDs). This involved either addition of csDMARD (Tofacitinib 5mg twice daily, a JAK I) in combination with MTX, or as monotherapy (in MTX-intolerant patients), based on individual patient factors and response.

The primary outcomes were set as DAS28-ESR scores, proportion of patients achieving remission (DAS28-ESR < 2.6) at 12 months, time to first remission, and treatment regimens at remission.
Remission was defined as achievement of DAS28-ESR < 2.6.[12]
The two groups were also compared for the adverse events observed during the study.

Data was analyzed using SPSS version 26. Descriptive statistics were used to summarize baseline characteristics, where quantitative variables were presented as mean and standard deviations, while qualitative variables were calculated as frequency and percentage. Independent t-test and Chi-square tests were applied to find the significance of difference between the two study groups where statistical significance was defined as a p-value <0.05

RESULTS

The mean age of patients in group LORA was 68.35±5.99 years (60-83 years) while the mean age in group EORA was 49±5.89 years (36-59 years). The group wise demographics, clinical findings and laboratory investigations are given in Table-I.

Table I

Demographics, clinical assessment and laboratory investigations (n=1340)

Demographics, clinical assessments and laboratory investigations		Group LORA (n=670)	Group EORA (n=670)
Age (Mean±SD) Years		68.35±5.99	49±5.89
Gender	Male n (%)	277 (41.34)	271 (40.45)
	Female n (%)	393 (58.66)	399 (59.55)
Duration of Disease (Mean±SD) Years		3.93±1.16	2.94±1.33
Treatment regimen at base line	Corticosteroids n (%)	86 (12.84)	108 (16)
	cs DMARD n (%)	29 (4.33)	21 (3.1)
	ts DMARD n (%)	47 (7)	34 (5.1)
	NSAID n (%)	217 (32.4)	249 (37.2)
Incidence of co-morbidities	Osteoarthritis n (%)	232 (34.6)	97 (14.5)
	Cardiovascular n (%)	138 (20.6)	62 (9.3)
	Diabetes n (%)	163 (24.33)	54 (8.1)
	Others n (%)	113 (16.9)	52 (7.8)
Number of Tender joints Median (Mean±SD)		16.84±2.19	17.16±2.05
Number of swollen joints Median (Mean±SD)		17.16±2.05	14.34±4.97
ESR (Mean±SD) mm/hour		48.31±1.86	48.78±2.53
hsCRP levels (Mean±SD) mg/lite		17.42±2.41	19.98±3.2
Patients with +ve RA Factor n (%)		483 (71.9)	497 (74.2)
SDAI Score (Mean±SD)		41.99±4.79	41.67±4.6
CDAI Score (Mean±SD)		40.01±4.73	39.66±4.5
DAS28-ESR Score (Mean±SD)		6.33±1.83	6.23±1.81

The details of regimen recorded for the two groups at the time of remission showed that, significantly more patients in group LORA were on MTX monotherapy (<0.0001), MTX+ Tofacitinib combination (0.04) and lesser on tofacitinib monotherapy (<0.0001). However, there was no statistically significant difference in the two groups in DAS28-ESR score achieved and the number of patients achieving DAS28-ESR <2.6 as shown in Table-II.

Table II

RA treatment regimen and the DAS28-ESR Score achieved, at the final follow up visit n=1340

Outcomes variables	Group LORA (n=670)	Group EORA (n=670)	p-value
RA treatment regimen			
MTX+ Tofacitinib n (%)	361 (54)	308 (46)	0.004
MTX monotherapy n (%)	208 (31)	174 (26)	0.04
Tofacitinib monotherapy n (%)	101 (15)	188 (28)	<0.0001
Final DAS28-ESR score and patients achieving remission			
DAS28-ESR score (Mean±SD)	1.85±0.73	1.8±0.77	0.22
Patients achieving DAS28-ESR <2.6 n (%)	534 (79.7)	526 (78.5)	0.59

Comparison of time to remission in patients achieving remission displayed no statistically significant variation between the two groups as shown in Table-III.

Table III

Time to achieve remission

Study groups	Time taken to remission (Mean±SD) months	p-value
Group LORA (n=534)	10.19±2.4	0.5
Group LORA (n=526)	10.29±2.4	

The data regarding adverse events showed different events among these two groups including incidences of withdrawal, serious infections, elevated lever enzymes, herpes zoster, acute infusion reaction, GI symptoms and malignancy, however, no significant differences were observed between these groups in terms of these events reported in this study as shown in table-IV.

Table IV

Incidences of adverse events (n=1340)

Adverse events	Group LORA (n=670)	Group EORA (n=670)	p-value
Serious infections n (%)	51 (7.6)	34 (5.1)	0.06
Elevated lever enzymes n (%)	27 (4)	41 (6)	0.08
GI symptoms n (%)	67 (10)	51 (7.6)	0.12
Acute infusion reaction n (%)	29 (4.3)	17 (2.5)	0.07
Serious or non-serious Herpes Zoster	6 (0.9)	10 (1.5)	0.31
Any type of malignancy	3 (0.4)	2 (0.3)	0.65
Withdrawal due to adverse event	7 (0.1)	8 (1.2)	0.8

DISCUSSION

The mean age in our study was 68.35±5.99 years (60-83 years) and 49±5.89 years (36-59 years) in group LORA and group EORA, respectively. The details of regimen recorded for the two groups at the time of remission showed that significantly more patients were on MTX monotherapy (p=0.04), MTX+ Tofacitinib combination

(0.004) and lesser on tofacitinib monotherapy (p<0.0001) in the group LORA compared to group EORA. There was no statistically significant difference in the two groups in DAS28-ESR score achieved and the number of patients achieving DAS28-ESR <2.6 at the completion of study. Comparison of time to remission in patients achieving remission showed no statistically significant difference among the two groups (p=0.5).

The treatment regimen, achievement of remission and time to achieve remission in LORA and EORA patients has been discussed in a number of publications, however, very few have discussed the comparison between these two groups.

Arnold MB et al. studied the 3 groups of RA patients diagnosed at young, middle and elderly ages. Older patients with > 64 years of age showed a distinct treatment and remission patterns than the other groups. The improvement assessed on DAS 28 was consistent among all age groups, however, older patients had higher baseline and 12-month DAS28 scores with lower remission rates (P < 0.003). Older patients were also reported to receive more DMARDs and steroids but fewer biologics, suggesting that age-specific treatment approaches influence the remission outcomes in RA management.[13] Tan TC et al. worked on the differences in the treatment and remission outcomes between LORA and EORA patients in an Asian cohort. LORA patients, defined by disease onset at ≥60 years, exhibited a greater number of comorbidities, poorer physical functioning, and worse Health Assessment Questionnaire score compared to patients with EORA. Despite similar disease activity levels, elderly patients received less intensive treatment, including fewer DMARDs due to co-morbidities and their poor overall health status. The outcomes emphasized the need for tailored treatment regimens to optimize remission and improve functional outcomes in RA.[14] In a comparative research of elderly-onset versus young-onset RA, significant differences emerged in disease presentation and treatment patterns. LORA patients presented with more acute onset and systemic symptoms (p<0.001), though seropositivity and radiographic erosions were uniform across the groups. LORA patients also demonstrated higher disease activity (DAS28, p=0.03) and functional impairment (p<0.001). MTX remained the primary treatment in both the groups, biological therapy was less frequently prescribed in LORA patients (30% vs. 47%, p=0.041), likely due to their higher comorbidity burden (84% vs. 37%, p<0.001).[15] Bobirca et al conducted a comparative study in Romania, between elderly-onset and young-onset RA. Both the groups initially received similar DMARD monotherapy with MTX being primary (EORA 61.5%, LORA 54.0%, p=0.602). EORA patients were more frequently on bDMRDS compared to LORA (69.8% vs 35.9%, p=0.001), correlating with better outcomes in EORA than the LORA group with higher remission rates (53% vs 23%, p=0.002).[16]

In a study performed by Horiuchi AC et al. in Brazil, the comparison between elderly-onset and younger-onset RA patients revealed distinct disease patterns with higher rates of rheumatoid factor positivity (p = 0.007), male predominance (p = 0.02), and demonstrated better functional outcomes with lower HAQ scores (p=0.04) in the LORA patients. Disease management approaches were consistent across the groups, with no marked differences in medication use as reported at the final follow up. While the age of onset influenced certain disease characteristics, it may not significantly impact treatment choices or extra-articular manifestations.[17]

Impact of age of onset on remission was expressed in a study conducted by Matsumoto T et al, where comparison was done between patients having onset of RA ≥ 75 years versus onset at < 75 years. A T2T strategy showed reduced remission in RA ≥ 75 years compared to those with < 75 years (32.7% vs 66.7%, respectively). Safety issues and comorbidities impacted adherence and outcomes in older patients.[18]

In a cohort study by LI X et al, comparing LORA and YORA patients, time to remission was uniform across the groups (HR=1.10, 95% CI: 0.90-1.34, p=0.36). However, at remission, LORA patients achieved control with simpler regimens, predominantly using single csDMARD (34% vs 27%), while YORA required more biologics/JAK inhibitors (27% vs 16%, p=0.004).[11]

Results of our study are in line with studies discussed above and showed that, with the similar treatment regimen in majority of patients, the use of JAK I was more common in the EORA group than the LORA group.[11,13,14,15] Results regarding time to remission was also comparable among the groups as shown in previous study done by LI X.[11]

The limitations of our study include, single-center study design and shorter duration of follow-up. Future studies with a multicenter approach and longer follow-up will contribute to this valuable data regarding treatment regimens and time to remission among these commonly reported groups of RA patients.

CONCLUSION

In conclusion, while the patients with LORA and EORA had differences in medication regimens when treated to target, where LORA patients were more frequently on MTX monotherapy or MTX+ Tofacitinib combination, there were comparable levels of disease activity outcomes or time to remission between the two groups. These findings suggest that the age of onset does not significantly impact the efficacy of standardized treatment regimens in achieving remission in RA patients.

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