Research article

Influencers of deterioration in patients with rheumatoid arthritis on DMARD therapy

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Abstract

Objective: To identify the socio-demographic, clinical and health care factors that influence deterioration to Disease Modifying Antirheumatic Drugs (DMARDS) in patients with Rheumatoid Arthritis (RA).

Methods: We conducted a prospective cohort study on RA patients diagnosed according to the ACR (1987) or ACR/EULAR criteria (2010). These patients were followed up in four rheumatology clinics in three counties in Kenya. A pre-coded questionnaire was used to capture socio-demographic and clinical characteristics of the patients. Baseline data was collected at the time of recruitment into the study. Patients were then followed up while on treatment with DMARDS and only those who had complete data at 3 months were included in the study analysis. The study outcome was defined using Disease Activity Score 28 (DAS-28) as either remission or Low Disease Activity (LDA) at 3 months follow-up. The Adherence in Chronic Disease Scale (ACDS) was used to assess the implementation of the treatment plan. Data analysis was carried out using Prism7 and SPSS version 25**,** p value of < 0.05 was considered statistically significant.

Results: Of the 206 patients included, the mean age was 51.2 ± 15.1 years with female predominance (91.3%). Majority (83.5%) had post primary education, only 35.9% had formal professional employment and 3% had medical insurance. At recruitment, nearly half of the included patients (47.6%) had an overall health assessment questionnaire disability index (HAQ-DI) score of > 2.5, indicating moderate to severe disability. The majority of patients had elevated baseline Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Most (90.3%) of the patients had a positive Rheumatoid Factor (RF) test at recruitment, and 58.5% of patient had a positive anti-Cyclic Citrullinated Peptide (Anti-CCP) test. Twelve percent, 62%, 10% and 16% of the patients had High Disease Activity (HDA), Moderate Disease Activity (MDA), Low Disease Activity (LDA) and remission respectively. Majority (94.2%) of patients were on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), 80.6% were on Conventional Disease Modifying Anti-Rheumatic Drugs (CsDMARDs) and 55% on systemic corticosteroids. The mean duration of follow-up was 4.6 months. During the follow-up, 37.9% found the system to be acceptable and 63.6% found the system to be problematic. Majority of the patients reported to have been adherent to therapy (7.8% were high adherence: 87% were moderate adherence). A total of 52 (27.7%) patients deteriorated (had severe disease activity at follow up). A high baseline of DAS-28 score (OR = 4.4, 95% CI 2.67-7.57, P<0.001) and non-adherence (OR=30.4, 95% CI 4.82-191.66, p<0.001) were identified as independent predictors of deterioration.

Conclusion: High baseline of DAS-28 and non-adherence are independent predictors of disease deterioration in patients with RA.

Key words: Rheumatoid arthritis, Disease activity score, Health assessment questionnaire, Adherence, High disease activity, Kenya

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis and joint destruction. The treatment of RA is based on Disease Modifying Antirheumatic Drugs (DMARDS) where methotrexate is the preferred initial DMARDS for RA[1]. The main objectives of this treatment are to reduce disease activity, prevent joint deformities, impaired function and disability. There are multiple treatments for RA: (csDMARDS, Janus Kinase inhibitors (JAKi), biological DMARDS (bDMARDS), and anti-CTLA-4)[2-5]. The first choice of treatment of RA is a (csDMARDs) such as methotrexate[2-4]. According to National Institute for Health and Care Excellence (NICE), patients who

do not respond to csDMARDs are eligible for biologic or targeted therapies. Three classes of biological DMARDs (bDMARDs) are available the most commonly prescribed being tumour necrosis factor α inhibitors (anti-TNF) therapy[3]. All these treatments are available in Kenya. Despite this wealth of pharmacological agents available for treatment of RA, a significant minority of patients still have an inadequate response leading to irreversible joint damage due to uncontrolled inflammation. We sought to identify the socio-demographic, clinical and healthcare factors that influence the deterioration to DMARDs in RA patients.

Materials and methods

This study was undertaken at four rheumatology clinics across Kenya: Kenyatta National Teaching and Referral Hospital (KNH) and Mater Hospital (MH) in Nairobi; Mombasa Hospital (MsaH) in Mombasa and Aga Khan University Hospital (AKUH) in Kisumu. The Rheumatology clinic at the KNH was the main study site. KNH is a hospital located in the capital city of Nairobi which has a capacity of 2,200-beds and serving clientele referred from all over Kenya. The other three hospitals (MH, MsaH and AKUH-Kisumu) have relatively smaller rheumatology clinics and were included to augment the main site and to increase sampling frame. This was a multi-center prospective cohort study conducted between June 2021 through to December 2022.

We included all RA patients diagnosed according to the ACR 1987 or ACR/EULAR 2010 classification criteria. The following treatment modalities were employed non-steroidal analgesics (NSAIDS), conventional Disease-Modifying Anti-Rheumatic Drugs (csDMARDS), biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDS), Janus Kinase inhibitors (JAKi) and corticosteroids. The patients were aged 18 years and above, who consented to the study, who were commenced on a therapy that remained constant for at least 3 months. We excluded severely ill patients who were unable to participate in the study at the time of data collection.

Prior to implementing the study, we obtained ethical clearance from KNH-UON Ethics, National Commission for Science, Technology, and Innovation (NACOSTI) and Research Committee. We also had clearance from the four clinical sites to access patient records. Informed consent was sought from the patients prior to participation. This form included a brief overview of the study and the researcher's contact information for further questions or clarifications. Respondents in the study were informed of their privacy and confidentiality throughout the study. Anonymity was maintained especially in the data presentation by coding of information instead of using of patients' identities. The data was securely stored in a password-protected computer folder. The investigator honored exclusive rights, charters, in addition to all forms of intellectual property. Additionally, the lead investigator did not accept the use of unverified data, methods, or results without prior authorization and cited all sources of information to avoid plagiarism. We used questionnaires to capture patient information. The questions were written according to Sekaran for which respondents recorded their answers within strictly defined alternatives[5]. The questionnaire contained both structured and unstructured questions designed to obtain valuable information about the patients. Every element in the questionnaire was adapted to address a precise objective, a research question or a hypothetical estimate of the required knowledge. Questionnaires were administered through face-to-face interviews by a trained medical officer. The same medical officer collected data in all the study sites. Adequate measures were put in place that mitigated the spread of COVID-19 infection by using appropriate clothing and maintaining a recommended social distancing in the community. The researcher ensured that a friendly atmosphere of trust and confidence was created to enable the respondents to discuss freely. The questionnaire contained sociodemographic and environmental characteristics, clinical characteristics, laboratory parameters and functional disability assessed using the Health Assessment Questionnaire Disability Index [HAQ-DI]). Adherence to treatment was assessed using the Adherence in Chronic Diseases Scale (ACDS) tool, which has been widely validated for use in adult patients on treatment for chronic diseases. The tool contains 7 questions: 1-5 are based on patient characteristics to treatment taking behavior; questions 6 and 7 show the doctor-patient connection that impair adherence. Each question is scored on a scale of 0 (never) to 4 (always) points. A total score of >26 points indicates high adherence to treatment, while scores 21-26 and <21 points are moderate and low respectively[7].

Results

Two hundred and six RA patients were included in our study. In the first step, we analyzed the association between the sociodemographic data (Table 1), clinical parameters and health care related factors, and the response to DMARD therapy in RA patients.

Table 1: Sociodemographic characteristics

Characteristic		Total
Age (years; mean, SD)	At diagnosis of RA	43.3 ± 14.4
	At enrollment into the study	51.2 ± 15.1
Sex (n, %)	Female	188 (91.3%)
	Male	18 (8.7%)
Age groups (years) (n, %)	< 40	47 (22.8%)
	40-49	46 (22.3%)
	50-59	43 (20.9%)
	≥60	70 (34%)
County (n, %)	Nairobi	187 (90.8%)
	Mombasa	9 (4.4%)
	Kisumu	10 (4.9%)
Education level (n, %)	None	8(3.9%)
	Primary level	26(12.6%)
	Secondary level	49 (23.8%)
	Tertiary level	123 (59.7%)
Housing (n, %)	Renting	137 (66.5%)
	Owning	65 (31.6%)
	Living without paying	4 (1.9%)
Payment for healthcare (n, %)	Government funding	3 (1.5%)
	Private insurance	3 (1.5%)
	Self-pay	196 (95.1%)
	Family support	4 (1.9%)
Occupation (n, %)	Unemployed	19 (9.2%)
	Student	6 (2.9%)
	Housewife	47 (22.8%)
	Businessperson	43 (20.9%)
	Farmer	17 (8.3%)
	Professional employment	74 (35.9%)
Income in Kenya Shillings (Kshs.)* (n, %)	<5,000	71 (34.5%)
	5,000-19,999	15 (7.3%)
	20,000-49,999	21 (10.2%)
	50,000-99,999	65 (31.6%)
	100,000-149,999	27 (13.1%)
	>150,000	7 (3.4%)
Smoking (n, %)	Yes	8 (3.9%)
	No	198 (96.1%)

* 1 US$ = Kshs. 140

Clinical characteristics

The mean HAQ-DI was 2.5±0.9 indicating moderate to severe disability. Nearly half (47%) of the included patients had a score > 2.5. Three patients (1.5%) had retroviral disease at enrolment. The mean Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) levels were 36.5±23.6 and 14.5±24.2 respectively, with majority of patients presenting with elevated levels (n=128, 62.1% and n=151, 73.3% respectively). Most of the patients had a positive Rheumatoid Factor (RF) test at recruitment (n=186 patients, 90.3%), while 113 (58.5%) patients had a positive anti-cyclic citrullinated peptide (Anti-CCP) test. At recruitment, the mean DAS28 score was 4.0±1.5. Majority (61.7%) had moderate disease (MDA) activity. A majority were on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (94.2%), and 55% had systemic corticosteroids. All were on a DMARD as follows csDMARDs (80.6%) and bDMARDs (11.7%). The most common csDMARD was leflunomide (48.1%) and bDMARDS was tocilizumab (7.3%) (Table 2).

Table 2: DAS28 score and drug therapies at recruitment stage

	Remission (DAS28 score <2.6)	33 (16%)
	Low disease activity (DAS28 score 2.6-3.2)	20 (9.7%)
	Moderate disease activity (DAS28 score 3.3-5.1)	127 (61.7%)
	High disease activity (DAS28 score >5.1)	26 (12.6%)
Drugs	NSAIDs	194 (94.2%)
	Steroids	113 (54.9%)
	Conventional synthetic DMARDs (csDMARDs)	166 (80.6%)
	Biological DMARDs (bDMARDs)	24 (11.7%)
bDMARDs	Tocilizumab	15 (7.3%)
	Infliximab	3 (1.5%)
	Rituximab	4 (1.9%)
	Golimumab	2 (1%)
	Adalimumab	2 (1%)
	Etanercept	1 (0.5%)
csDMARDs	Leflunomide	99 (48.1%)
	Hydroxychloroquine	95 (46.1%)
	Methotrexate	75 (36.4%)
	Sulphasalazine	25 (12.1%)

Clinical characteristics and laboratory at follow-up

The mean duration of follow-up was 140±61 days (4.6 months). At follow up compared with baseline, there was a significant reduction in the proportion of patients with elevated ESR and CRP and those with moderate/ severe disability (47.6% vs 42.2%, p<0.001). and a slight reduction in the mean DAS28 score (4.0±1.5 vs 3.9±1.2, p=0.502) (Table 3).

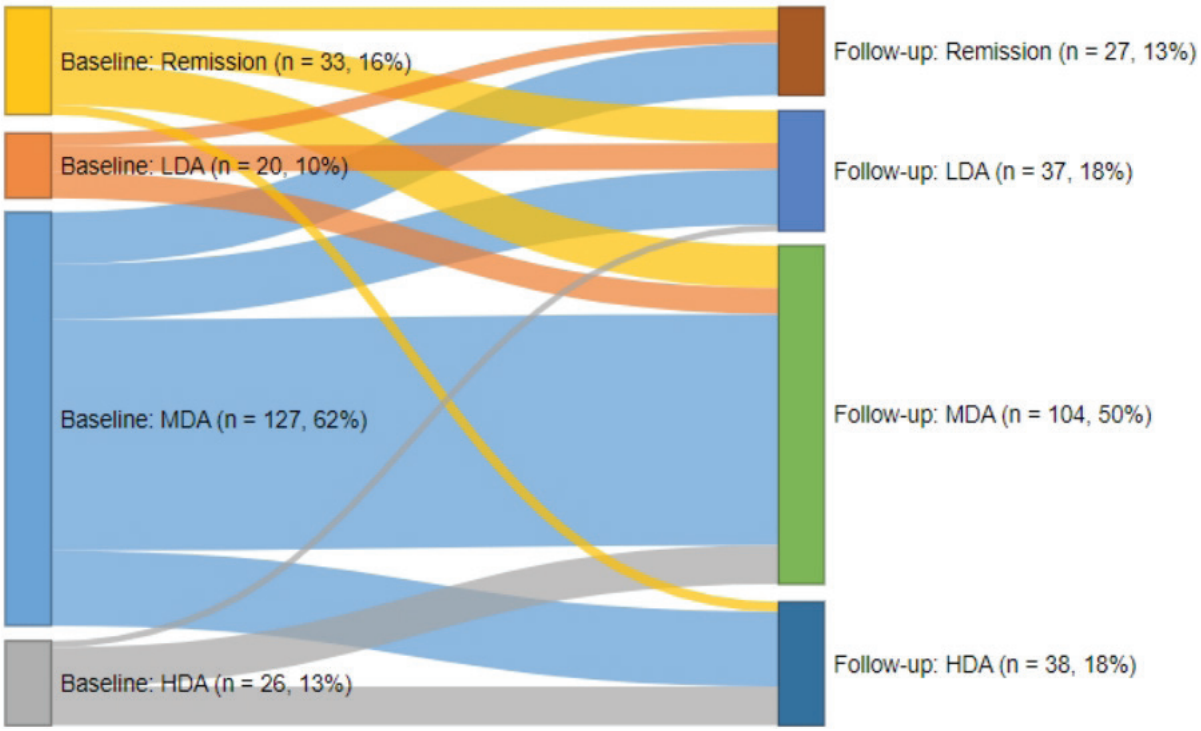
Table 3: Clinical and laboratory characteristics of patients at follow up

Variable		Baseline	Follow-up	P-value
ESR	Normal	78 (37.9%)	89 (43.2%)	p<0.001
	Elevated	128 (62.1%)	117 (56.8%)	
CRP	Normal	55 (26.7%)	129 (64.5%)	p=0.002
	Elevated	151 (73.3%)	71 (35.5%)	
HAQ-DI score	No disability	108 (52.4%)	119 (57.8%)	p<0.001
	Disability	98 (47.6%)	87 (42.2%)	
DAS-28 severity	Remission/LDA	53 (25.7%)	64 (31.1%)	p<0.001
	MDA/HDA	153 (74.3%)	142 (68.9%)	

Legend: ESR- Erythrocyte sedimentation rate; CRP- C reactive protein; LDA-Low disease activity; MDA-Moderate disease activity; HAD- High disease activity; DAS-28- Disease activity severity 28 score; HAQ-DI-Health assessment questionnaire disability index

The trajectory of disease activity is shown in Figure 1, illustrates the trajectory at which disease progression developed from the time of drug initiation. Overall, 47.6% remained in the same disease severity category, around 24.8% demonstrated improvement by shifting to a less severe disease category, while 27.7% deteriorated into a more severe disease category.

Figure 1: Trajectory of disease severity for included patients

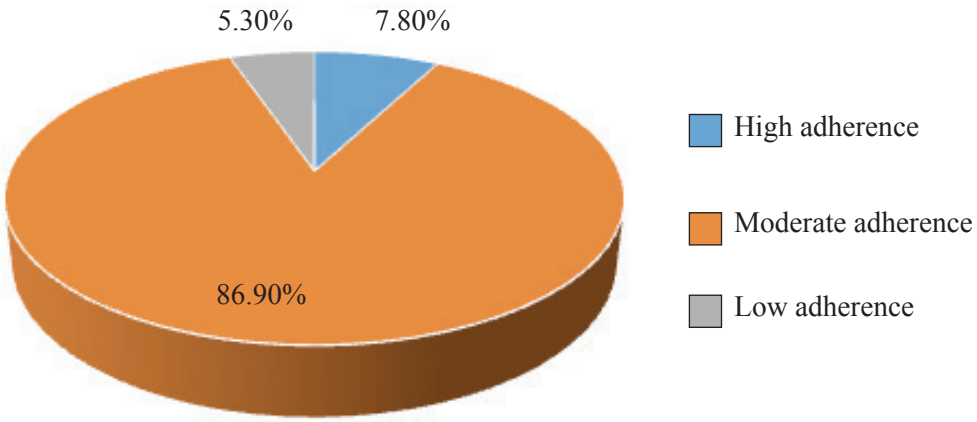


Legend: LDA- Low disease activity; MDA- Moderate disease activity; HAD- High disease activity

Adherence

Majority of the patients were adherent to therapy (Figure 2).

Figure 2: Patient adherence



Characteristics of patients with clinical deterioration at follow-up

This was an exploratory analysis to determine factors associated to clinical deterioration at 3-months follow-up. Fifty-seven patients (27.7%) had clinically deteriorated (had more severe disease at follow-up), whereas 98 (47.6%) patients remained stable and within the same severity category and 51 (24.8%) patients demonstrated improvement. Comparison of sociodemographic features shown in (Table 1) between patients who deteriorated

vs. those who improved/remained within same disease severity category revealed no difference. By contrast those who deteriorated were more likely at baseline to have elevated CRP, ESR, higher disease activity score, a greater degree of functional disability and higher rates of non-adherence (Table 4).

Table 4: Comparison of clinical and healthcare system-associated characteristics between patients who deteriorated vs those who improved/remained within same disease severity category

Characteristic		Improved/same disease severity category (n=149 patients)	Deteriorated (n=57 patients)	P-value
Duration of disease (years)	(mean, SD)	7.3±7.6	7.7±10.91	p=0.779[#]
Retroviral disease	Yes	2 (1.3%)	1 (1.8%)	p=0.825[£]
	No	147 (98.7%)	56 (98.2%)	
ESR	Elevated	50 (33.6%)	28 (49.1%)	P=0.041[£]
	Normal	99 (66.4%)	29 (50.9%)	
CRP	Elevated	33 (22.1%)	22 (38.6%)	p=0.017[£]
	Normal	116 (77.9%)	35 (61.4%)	
Rheumatoid factor	Positive	136 (91.2%)	50 (87.7%)	p=0.245[£]
	Negative	13 (8.8%)	7 (12.3%)	
Anti-CCP	Positive	85 (57.0%)	28 (49.1%)	p=0.510[£]
	Negative	56 (43.0%)	24 (50.9%)	
Baseline DAS-28 Score		4.3±1.4	3.1±1.1	p<0.001[#]
Baseline HAQ-DI (disability)	Score	2.6±0.9	2.3±0.8	p=0.042[#]
Non-biologic DMARDS	Yes	133 (89.2%)	49 (85.9%)	p=0.510[£]
	No	16 (10.8%)	8 (14.1%)	
Biologic DMARDS	Yes	33 (22.1%)	7 (12.3%)	p=0.120[£]
	No	116 (77.9%)	50 (87.7%)	
NSAIDS	Yes	140 (94.0%)	54 (94.7%)	p=0.565[£]
	No	9 (6.0%)	3 (5.3%)	
Steroids	Yes	85 (57.1%)	28 (38.6%)	p=0.349[£]
	No	64 (42.9%)	29 (50.9%)	
Adherence	Low	4 (2.7%)	7 (12.3%)	p=0.011[£]
	High	145 (97.3%)	50 (87.7%)	
EUROPEP	Good/acceptable	53 (35.6%)	22 (38.6%)	p=0.471[£]
	Problematic	96 (64.4%)	35 (61.4%)	

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; DAS-28: Disease activity score-28; HAQ-DI: Health assessment questionnaire disability index; DMARDS- disease modifying anti-rheumatic drugs, NSAIDS: Non-steroidal anti-inflammatory drugs

Predictors of deterioration

In unadjusted (univariate) regression analysis, none of the socioeconomic factors (Table 1) were associated with a deterioration in clinical state. However within the clinical and healthcare-system associated predictors of deterioration an elevated baseline ESR (OR=1.91, 95% CI 1.02-3.56, p=0.041), elevated baseline CRP (OR=2.21, 95% CI 1.14-4.26, p=0.018), a higher baseline disease activity (DAS-28 score) (OR=2.87, 95% CI 2.00-4.01, p<0.001), higher baseline functional disability (OR=1.44, 95% CI 1.00-2.06, p=0.048) and non-adherence (OR=5.08, 95% CI 1.43-18.07, p<0.001) were associated with higher odds of deterioration.

Adjusted (multivariate) analysis

Variables that were significant at univariate analysis were used to construct a multivariate (adjusted) analysis. Only a higher baseline disease activity (DAS-28 score) (OR=4.49, 95% CI 2.67-7.57, p<0.001), and non-adherence (OR=30.40, 95% CI 4.82-191.66, p<0.001) persisted as independent predictors of deterioration.

Discussion

It is well established that the early initiation of DMARDs in RA results in better outcomes and less disease activity and ideally in a specialist rheumatology setting[8-10]. It is important therefore to identify factors which might mitigate against improvement leading to an adverse outcome. We have identified a number of those active in our setting and summarized in Table 5.

Table 5: Factors that significantly led to deterioration

Characteristic	P-value
Having longer duration of disease	p<0.004
Elevated baseline ESR	p<0.001
Elevated baseline CRP	p=0.046
Higher baseline degree of functional disability	p<0.001
Higher DAS-28 disease activity score	p<0.001
Higher rates of non-adherence	p<0.011

From the analysis of 206 patients, there were 57 (27.7%) patients who deteriorated and of these, a majority depicted significant baseline functional disability. Studies have shown that higher baseline functional disability leads to inability to work, absenteeism, retirement on grounds of ill-health and unemployment potentially leading to economic and financial vulnerabilities, decreased quality of life and increased mortality[11]. Studies have also shown that scores for higher baseline of Functional Disability (FD) are linked to higher levels of pain scores[12].

With chronicity of disease there is a higher likelihood of increased functional disability. In our study, deterioration was also associated with a longer duration of disease. The effects of long duration of disease have a ripple effect in deterioration and applies in most chronic disease states. Shifts in the inflammatory response mechanisms may result in a breakdown of immunological tolerance leading to deterioration of RA including the risk of developing comorbidities[13].

A Japanese study established that at enrolment the mean disease duration of RA was significantly longer in patients who experienced Cardiovascular Events (CVEs) compared to those who did not, confirming the now well-established fact that RA is an independent risk factor CVEs[14].

Our study recorded significant elevated baseline serum ESR (p<0.001) and elevated baseline serum CRP (p<0.046) values in those who deteriorated. Even though ESR and CRP measurements are still not considered perfect in immunological assays, they still hold a place in the diagnosis and management of RA. They are still an important biomarker which are included in the ACR/EULAR classification of 2010 classification criteria for RA[9]. Several studies have demonstrated nexus between serum ESR and serum CRP elevation, in particular as markers for radiographic and functional deterioration[10]. Raised ESR is believed also to offer a superior prediction of clinical outcomes in early RA compared to CRP which may be an independent indicator in the later stages of disease[10].

Studies have shown that persistent high DAS28-P score distinguish between poor patient global assessment and excessive treatment escalation in early RA, suggesting underlying non-inflammatory pain contributing to a higher disease activity score[15]. Our study recorded a significantly higher DAS28 (p<0.001). Ochola *et al*[16] showed that there was a significant correlation between the DAS28 score and RA deterioration, in this study and in our study, more than half of the patients in the study had severe RA when the DAS28-ESR score was used. Buckman *et al*[17] also reported a high DAS28-ESR score value > 5.1 which had deleterious effects on RA patients, many of the patients in their series deteriorated with poor outcomes. They also found other factors associated with RA progression namely marital status (p = 0.041), disease duration (p = 0.04) and family complaints (p = 0.019), but these parameters were not assessed in our study. The other clinical and laboratory characteristics assessed in our study were not significantly associated with disease progression.

Overall adherence to DMARD medication in our study was good. Those who deteriorated had significantly higher rates of non-adherence (12.3% vs 2.7%, p=0.011). Adherence to medication. is influenced by numerous factors, classified by the WHO into five dimensions socioeconomic, healthcare system, patient condition, and therapy[11]. Adherence is important to reaching the desired

treatment outcome especially at the start of treatment[18]. However, in RA, medication adherence is highly variable with reports ranging from 22% (underuse) to 107% (overuse)[19]. Overall non-adherence in RA can lead to treatment failure, delayed recovery, accelerated disease progression and the need for more aggressive treatment[19,21]. The consequences of non-adherence will not only affect the patient's disease activity, but also the rheumatologist's treatment decisions, and may lead to higher health care costs[19].

Conclusion

The main predictors of RA patient deterioration have been associated with higher degree of functional disability, longer duration of disease, elevated serum ESR and CRP, higher DAS28 score and higher rates of non-adherence.

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References

1. Duong SQ, Crowson CS, Athreya A, Atkinson EJ, Davis JM, Warrington KJ, *et al*. Clinical predictors of response to methotrexate in patients with rheumatoid arthritis: a machine learning approach using clinical trial data. *Arthritis Res Ther.* 2022; **24**(1):162.
2. Majorczyk E, Mazurek-Mochol M, Pawlik A, Kuśnierczyk P. Clinical factors and the outcome of treatment with methotrexate in rheumatoid arthritis: Role of rheumatoid factor, erosive disease and high level of erythrocyte sedimentation rate. *J Clin Med*. 2022; **11**(20):6078.
3. Taylor PC, Askari A, Choy E, Ehrenstein MR, Else S, Nisar MK. Approaches to optimising access to NICE-approved biologic anti-TNFs for patients with rheumatoid arthritis with moderately active disease. *BMC Med.* 2023; **21**(1):55.
4. Cherlin S, Plant D, Taylor JC, Colombo M, Spiliopoulou A, Tzanis E, *et al*. Prediction of treatment response in rheumatoid arthritis patients using genome-wide SNP data. *Genet Epidemiol.* 2018; **42**(8):754–771.
5. (PDF) B Research Methods ForBus A Skill Building Approach 7e2016UmaSekaran, RogerBougie Wiley | fahmi malik - Academia.edu [Internet]. [cited 2023 Aug 16]. Available from: https://www.academia.edu/38338906/B_Research_Methods_ForBus_A_Skill_Building_Approach_7e2016UmaSekaran_RogerBougie_Wiley
6. Dimova R, Stoyanova R, Keskinova D. The EUROPEP questionnaire for patient's evaluation of general practice care: Bulgarian experience. *Croat Med J*. 2017; **58**(1):63–74.
7. Kosobucka A, Michalski P, Pietrzykowski Ł, Kasprzak M, Obońska K, Fabiszak T, *et al.* Adherence to treatment assessed with the adherence in chronic diseases scale in patients after myocardial infarction. *Patient Prefer Adherence*. 2018; **12**:333.
8. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, *et al.* Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum*. 2000; **43**(1):30–37.
9. Shams S, Martinez JM, Dawson JRD, Flores J, Gabriel M, Garcia G, *et al.* The therapeutic landscape of rheumatoid arthritis: Current state and future directions. *Front Pharmacol.* 2021; **12**:680043.
10. Roodenrijs NMT, Welsing PMJ, Van Roon J, Schoneveld JLM, Van Der Goes MC, Nagy G, *et al*. Mechanisms underlying DMARD inefficacy in difficult-to-treat rheumatoid arthritis: a narrative review with systematic literature search. *Rheumatology*. 2022; **61**(9):3552–66.
11. Whitman A, Lew ND, Chappel A, Aysola V, Zuckerman R, Sommers BD. Addressing social determinants of health: Examples of successful evidence-based strategies and current federal efforts. *Off Heal Policy*. 2022; **1**:1-30.
12. Meesters J, Verhoef J, Tijhuis G, Vliet Vlieland T. Functional disability in patients with rheumatoid arthritis admitted for multidisciplinary rehabilitation from 1992 to 2009. *Rheumatology*. 2013; **52**(10):1879–83.
13. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. *Immunity*. 2017; **46**(2):183–196.
14. Masuda H, Miyazaki T, Shimada K, Tamura N, Matsudaira R, Yoshihara T, *et al.* Disease duration and severity impacts on long-term cardiovascular events in Japanese patients with rheumatoid arthritis. *J Cardiol.* 2014; **64**(5):366–370.
15. Pisaniello HL, Whittle SL, Lester S, Menz F, Metcalf R, McWilliams L, Hill CL, Proudman S. Using the derived 28-joint disease activity score patient-reported components (DAS28-P) index as a discriminatory measure of response to disease-

modifying anti-rheumatic drug therapy in early rheumatoid arthritis. *BMC Rheumatol*. 2022; **6**(1):67. doi: 10.1186/s41927-022-00299-3. PMID: 36376988; PMCID: PMC9664777.

16. Ochola B, Nankabirwa J, Buwembo W, Kaddumukasa M, Mayanja-Kizza H. The Clinical presentation and factors associated with disease severity of rheumatoid arthritis in Uganda: A cross-sectional study. *Open Access Rheumatol*. 2022; **14**:75-86. doi: 10.2147/OARRR.S361454. PMID: 35535352; PMCID: PMC9078424.
17. Buckman TA, Sakyi SA, Yeboah-Mensah K, Antwi MH, Darban I, Owusu-Brenya L, *et al.* Demographic, clinical profile of rheumatoid arthritis patients and their association with disease severity in Ghana. Pal R, editor. *Int J Rheumatol*. 2024; **2024**:1–9.
18. Li L, Cui Y, Yin R, Chen S, Zhao Q, Chen H, *et al*. Medication adherence has an impact on disease activity in rheumatoid arthritis: a systematic review and meta-analysis. *Patient Prefer Adherence.* 2017; **11**:1343–56.
19. Curtis JR, Bykerk VP, Aassi M, Schiff M. Adherence and persistence with methotrexate in rheumatoid arthritis: A systematic review. *J Rheumatol.* 2016; **43**(11):1997–2009.
20. Donneyong MM, Chang TJ, Jackson JW, Langston MA, Juarez PD, Sealy-Jefferson S, *et al*. Structural and social determinants of health factors associated with county-level variation in non-adherence to antihypertensive medication treatment. *Int J Environ Res Public Health*. 2020; **17**(18):6684.
21. Van Den Bemt BJ, Zwikker HE, Van Den Ende CH. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. *Expert Rev Clin Immunol.* 2012; **8**(4):337–351.