Adherence to disease modifying anti-rheumatic drugs among rheumatoid arthritis patients attending the Kenyatta National Hospital Rheumatology Clinic

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Abstract

Background: Rheumatoid Arthritis (RA) is a chronic multi-systemic disease characterised by inflammation of the synovial membranes of the joints. The cornerstone of treatment is with Disease Modifying Anti Rheumatic Drug (DMARD) therapy which includes synthetic and biologic agents. Adherence to RA treatment can be challenging as management requires a complex long-term interplay between the treating physician, medications used, the patient as well as their families and care-givers. Multiple factors contribute to variable adherence to therapy leading to treatment goals not being met. Assessing treatment adherence is therefore key to identifying and addressing the root causes of non-adherence.

Objective: To evaluate treatment adherence and clinical disease activity among rheumatoid arthritis patients attending the Kenyatta National Hospital Rheumatology Outpatient Clinic.

Methods: This was a descriptive cross-sectional study carried out at the Kenyatta National Hospital Rheumatology Outpatient Clinic. We recruited patients over the age of 18 years with a diagnosis of rheumatoid arthritis as diagnosed according to the 2010 ACR criteria on file and who had been on at least one DMARD for at least three months. The study tools that were used included a study proforma, the 5 item compliance questionnaire of rheumatology (CQR-5) to assess adherence and the Clinical Disease Activity Index (CDAI) to assess disease activity.

Results: A total of 97 patients, were recruited, 84.5% of whom were female and the mean age was 53.9 years. The overall level of adherence was 49.5% with a mean CQR-5 score (SD) of 15.8 (1.7). Moderate disease activity was noted in 85 (87.6%), patients 5 (5.2%) patients had low disease activity while 7 (7.2%) patients had high disease activity. No patient scored low enough to be categorized as being in remission. There was a significant association between age less than 62 years and adherence to DMARD therapy (p=0.032).

Conclusion: The level of adherence to DMARD therapy was lower than global averages and WHO recommendations. Most patients had moderate to high disease activity while no patients were found to be in remission. There was no statistically significant association between adherence to medication and disease activity.

Key words: Rheumatoid Arthritis, Adherence, Disease activity, Nairobi, CQR-5

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease of unknown aetiology. While it has several manifestations, it has a predilection for the joints wherein it causes a symmetrical polyarthritis which may initially be monoarticular. It is the commonest cause of chronic inflammatory arthritis and has an estimated worldwide prevalence of 0.5-1% [1,2]. Prevalence of RA in the Kenyan population is unknown but projections based on studies done throughout the continent estimate the prevalence to be around 0.43% [3].

In the list of conditions ranked according to the amount of disability attributed, RA sits at number 42 with a global economic burden of 5.8 billion U.S. dollars annually[4].

Apart from the economic impact, RA has been noted to cause increased mortality mainly through cardiovascular disease. This increased risk is postulated to be due to vascular damage associated with inflammation seen in the disease. An increased risk of development of lymphomas, skin cancer and lung cancer (perhaps due to the shared risk factor of smoking) has also been noted[1].

A 2003 World Health Organisation (WHO), report on medication adherence observed that improving adherence to

medical treatment may have a far greater impact on improving population health than any advance in specific treatments. This report also estimated the adherence level in non-communicable diseases to be at 50% [5].

Non-adherence to chronic therapies is rampant and costly. Estimates suggest that it costs 300 billion U.S. dollars annually and leads to the need for formulation of new therapies when existing treatments are shown to be ineffective yet the problem is not in the medication as such but rather in the adherence to treatment regimens. Aside from the economic impact, non-adherence also leads to reduced quality of life and relapses[4,6]. It has been noted as well that upto a third of all hospital admissions can be attributable to medication non-adherence [7].

The need for consistent therapy is highlighted by eight out of ten patients developing joint malalignment and almost half noted to have reduced work capacity within ten years of disease onset[2,8]. While early diagnosis and treatment prevents disease progression in upto 90% of patients, once significant joint damage has accumulated it leads to permanent disability such that even achieving clinical disease remission then does little by way of improving functional status. Permanent disability is caused more by cartilage than bone damage[2].

The level of adherence to RA treatment in the Kenyan population is not known. It is well known that DMARDs facilitate achievement of remission in upto 90% of patients[2]. Despite an increase in utilisation of DMARDS, remission rates in Kenya have remained low as was found in a 2009 study by Owino *et al*[9]. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease[9]. Ndirangu *et al*[10], in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease. In a 2017 study at KNH, Olago-Rakuomi *et al*[3] found that in spite of a majority of patients being on DMARDS (86%) most of the patients still had active disease with only 3% having achieved remission. Non-adherence may be a reason for the incongruence between DMARD therapy and disease activity seen in our setup. It is therefore important to study treatment adherence to discern the cause of this discrepancy.

Progression of RA has been linked to increased clinical disease activity. Sub-clinical inflammation as seen by imaging modalities such as ultrasound has not been shown to cause disease progression[1].

Clinical assessments include joint counts (swollen and tender), global assessments of functioning (patient's and physician's) and inflammatory biomarkers (Erythrocyte Sedimentation Rate and C-Reactive Protein). These are then aggregated in various permutations to form clinical indices such as the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Health Activity Questionnaire and the Disease activity score 28 (DAS28), among others. These tools are indispensable in the treat-to-target strategy employed in the management of rheumatoid arthritis where the goal is disease remission.

In the Kenyan population Ndirangu *et al*[10] found, in a sample of 106 patients, a median Clinical Disease Activity Index (CDAI) score of 11.0 which was indicative of moderate disease activity. They also found that only 10% of patients were in remission.

A systematic review by Li et al [11] in 2017 looked at the correlation between adherence and disease activity. They included seven studies with a total sample size of 1963 patients and found a significant difference in Erythrocyte Sedimentation Rate (ESR) and tender joint count, both indicators of active disease, between adherent and non-adherent patients. They concluded that RA patients with higher adherence have lower disease activity.

The level of adherence to RA treatment in the Kenyan population is unknown. Despite increase in utilisation of DMARDS, remission rates in Kenya have remained low as was found in a 2009 study by Owino *et al*[9]. From 60 patients recruited 46.7% of patients were on DMARDs yet 88% were found to have active disease[9]. Ndirangu *et al*[10], in 2016, found that while 86.5% of patients were on DMARDS 56-65% still had active disease. It is well known that DMARDs facilitate achievement of remission in up to 90% of patients[2]. Non-adherence may be a reason for the incongruence between DMARD therapy and disease activity seen in our setup.

Materials and methods

Study design: We carried out a questionnaire based descriptive cross sectional study.

Study site: The study was carried out at the Kenyatta National Hospital's (KNH) Rheumatology Outpatient Clinic (ROPC) in Nairobi, Kenya. KNH is one of two national referral hospitals in the country and runs its specialised rheumatology clinic every Thursday afternoon. New patients are seen by consultant rheumatologists from KNH and the University of Nairobi while patients on follow-up are seen by University of Nairobi Internal Medicine residents in consultation with the rheumatologists.

Study population: This consisted of patients with a diagnosis of rheumatoid arthritis based on the American College of Rheumatology attending the ROPC at KNH.

Patient selection

Inclusion criteria: We screened patient records for adult male and female patients with a diagnosis of rheumatoid arthritis on file. They also had to have been on active treatment consisting of at least one DMARD and been on follow up for at least three months. Patients should have been able to fill the questionnaire in English or Kiswahili or be accompanied by an individual who could aid them in this. Qualifying patients who gave informed consent were included in the study.

Exclusion criteria: Any patients not fulfilling any of the above criteria.

Sample size estimation: Given a population of 125 patients (N) with a diagnosis of RA attending the KNH ROPC and using an estimated adherence rate (p) of 65% 19, the estimated sample size (n) was calculated using the Fischer's equation and was found to be a minimum of 95 patients.

Sampling method: We carried out consecutive enrollment of patients who fulfilled the inclusion criteria until sample size was achieved.

Clinical methods: The principal investigator and a trained research assistant extracted relevant data from the patient file onto the study form and thereafter administered the CQR to eligible patients. Thereafter a clinical exam was conducted which entailed examining the patients peripheral joints for swelling and tenderness as well as obtaining a patient and physician global assessment of functioning. These measures were then used to fill in the clinical disease activity index part of the study form.

Study instruments: The study instruments that were used include the CQR-5 which is an abbreviated form of the only questionnaire validated in assessing adherence in rheumatoid arthritis, the CQR-19. It is a 5 item tool with responses ranked on a likert scale from 1- completely agree to 4-completely disagree. It consists of questions 2,3,5,6 and 17 of the CQR-19. The tool was translated into the Kiswahili language using the forward and back translation method by a professional translation service located in Nairobi.

The Clinical Disease Activity Index (CDAI) was used to assess disease activity. It has 2 objective parameters consisting of the swollen and tender joint counts each out of 28 and 2 subjective parameters including the physician global assessment of function as well as the patient global assessment of function each of which is scored out of ten. The total out of a score of 76 is used to grade disease activity. This score does not require measurement of an Acute Phase reactant and has been shown to be comparable to the SDAI (Simplified Disease Activity Index) and DAS-28 (Disease Activity Scale) in assessing disease activity[9,12]. Demographic data and clinical characteristics were extracted from patient files.

Ethical considerations: Patients were recruited upon giving informed consent by signing the informed consent form. The study was undertaken after obtaining approval from the Ethics and Research Council of the University of Nairobi and Kenyatta National Hospital.

Data analysis: Data was checked for completeness and free of error prior to entry into Microsoft Excel 2017 spreadsheet. Thereafter it was exported to the Statistical Package for Social Sciences version 23.0. Demographic and clinical characteristics of the patients that are categorical were analysed as frequencies and percentages, while the continuous data was analysed as means with standard deviation or median with interquartile range. The CQR5 score was calculated out of 20 with a score of 16/20 and above indicative of adherence and a score below 16 indicating non-adherence. The level of adherence to RA treatment among patients was calculated as a proportion of those adhering over the total sample size and reported as a percentage. Clinical disease activity according to CDAI score was assessed as follows; a score of 0.0 to 2.8 indicates remission, 2.9-10.0 low disease activity,10.1 to 22 moderate disease activity and 22.1 to 76.0 high disease activity. CDAI grades were analysed as frequencies and percentages. The link between RA adherence and clinical disease activity was analysed with the use of Chi-square test while the link difference in mean CDAI scores between adherent and non-adherent groups was assessed using the independent Student t test. The predictors of adherence were analysed with the use of Chi-square tests for categorical data, and with independent Student t-test for continuous data, to compare between adherent and non-adherent groups.

Results

Ninety seven patients were recruited into the study after exclusion of three patients out of 100 screened who declined to give consent.

Socio-demographic characteristics: Table 1 shows the sociodemographic characteristics of the sample population of 97 patients. The mean (SD) age was 53.9±15.4 years with a range of 22-82 years. Majority of the patients were female; 82 (84.5%). Married patients formed 60.8% of the study population. Patients whose residence was primarily rural were 58.8% and 94.8% of patients had at least attended primary school.

Clinical characteristics: As demonstrated in Table 2, comorbid conditions were present in more than 79 patients with the median number of comorbidities (IQR) being 2 (2-3). Rheumatoid factor was positive in 96.9% of patients while 52.6% were positive for Anti-CCP and 4.1% were Anti-Nuclear Antibody (ANA) positive. Both RF and Anti-CCP were present in 48.4% of patients. ANA was positive in 5 patients, 4 of whom were RF positive and 1 was anti-CCP positive.

Only five patients were on DMARD monotherapy, while a majority of the patients, 68, were on dual therapy. Five patients were on biologic DMARDs with all of them taking conventional DMARDs concurrently. Methotrexate was the most commonly prescribed DMARD at 93.8%. The number of medications used by each patient ranged from 2-9 with a median of 6.

Level of adherence to DMARD therapy: The main objectives of the study were to determine the levels of adherence to therapy and disease activity among patients

Table 1: Socio-demographic characteristics

Variable	Frequency (%)
Sex	
Male	15 (15.5)
Female	82 (84.5)
Age in years	
Mean (SD)	53.9 (15.4)
Min-max	22.0-82.0
Marital status	
Single	38 (39.2)
Married	59 (60.8)
Primary residence	
Rural	57 (58.8)
Urban	40 (41.2)
Level of education	
None	5 (5.2)
Primary	35 (36.1)
Secondary	34 (35.1)
Tertiary	23 (23.7)

Table 2: Clinical characteristics

Variable	Frequency (%)
Number of comorbidities	
Median (IQR)	2 (2-3)
Seropositivity	
Anti-cyclic citrullinated peptide antibody (Anti-CCP)	51 (52.6)
Rheumatoid factor	94 (96.9)
Anti-nuclear factor	4 (4.1)
Class of DMARDS	
Conventional	92 (94.9)
Both	5 (5.1)
Type of DMARDS	
Methotrexate	91 (93.8)
Hydroxychloroquine	73 (75.3)
Leflunomide	33 (34.0)
Sulfasalazine	9 (9.3)
Rituximab	2 (2.1)
Tofacitinib	2 (2.1)
Adalimumab	1 (1.0)
Total number of DMARDS	
Median (IQR)	2 (2-2.5)
Total number of medications	
Median (IQR)	7 (6-7)

Table 3: Assessment of adherence to RA drugs using CQR-5 tool

Variable	Frequency (%)
Adherence level	
Mean score (SD)	15.8 (1.7)
Min-max	13.0-20.0
Category, n (%)	
Adherent	48 (49.5)
Non-adherent	49 (50.5)

Table 4: CDAI

CDAI	
Mean (SD)	17.8 (4.3)
Min-max	4.0-29.0
Grade, n (%)	
Low	5 (5.2)
Moderate	85 (87.6)
High	7 (7.2)

Table 5: Association between disease activity and adherence to DMARDs

Variable	Adherence status		OR (95% CI)	P value
	Adherent (n=48)	Non-adherent (n=49)		
CDAI				
Mean score (SD)	17.1 (4.5)	18.6 (4.0)	-	0.082
Grade, n (%)				
Low	3 (6.3)	2 (4.1)	1	-
Moderate	41 (85.4)	44 (89.8)	0.6 (0.1-3.9)	0.612
High	4 (8.3)	3 (6.1)	0.9 (0.1-9.2)	0.921

Table 6: Correlation between clinical and demographic factors and adherence to DMARD therapy

Variable	Adherence status		OR (95% CI)
	Adherent (n=48)	Non-adherent (n=49)	
Sex			
Male	9 (18.8)	6 (12.2)	0.60(0.20-1.85)
Female	39 (81.3)	43 (87.8)	
Mean age in years (SD)	52.3 (13.7)	55.5(16.8)	-
Age group			
Old (>62)	10	20	2.62
Young (<62)	38	29	
Marital status			
Single	15 (32.2)	23 (46.9)	0.51 (0.22-1.17)
Married	33 (68.8)	26 (53.1)	
Residence			
Rural	27 (56.3)	30 (61.2)	1.22(0.55-2.76)
Urban	21 (43.8)	19 (38.8)	

Variable	Adherence status		OR (95% CI)
	Adherent (n=48)	Non-adherent (n=49)	
Level of education			
Below primary	19	21	1.14(0.51-2.57)
Above Secondary	29	28	
Comorbidities			
Median number (IQR)	2 (2-3)	2 (2-3)	-
DMARDS			
Median number (IQR)	2 (2-2.5)	2 (2-2)	-
Total medications			
Median number (IQR)	6 (6-7)	7 (6-7)	-

with rheumatoid arthritis attending the KNH ROPC. Table 3 demonstrates that the overall adherence level we found; as a proportion of those patients who scored more than 16/20 on the CQR-5, was 49.5%.

Clinical disease activity: Clinical disease activity scores as shown in Table 4 demonstrate a mean (SD) CDAI score of 17.8 (4.3). Most patients were classified as having moderate disease activity (87.6%) while 5.2% and 7.2% were found to have low and high disease activity respectively. None of the patients were found to be in remission.

Correlation between CDAI and adherence to DMARD therapy: Chi square test was used to analyse the correlation between CDAI grades and adherence to DMARD therapy. Odds ratios (p values) of 1.0, 0.6 (0.6) and 0.9 (0.9) were obtained for low, moderate and high disease activity respectively showing no significant difference between adherent and non-adherent groups. However an independent student t test run to compare the mean CDAI values between adherent and non-adherent groups was found to trend towards significance with a p-value of 0.08 as shown in Table 5.

Correlation between clinical and demographic factors and adherence to DMARD therapy: We found a significant difference in adherence between patients aged less than and more than 62 years with the younger group having a higher level of adherence (OR 2.62 p 0.036). No other significant correlation was found between clinical and demographic factors between patients who were adherent to and those that were non-adherent to DMARD therapy. However, there was a tendency toward significance (p=0.11) when comparing adherence between single and married patients with the latter having a higher level of adherence. This is demonstrated in Table 6.

Discussion

The main objective of this study was to determine the levels of adherence to DMARD therapy in a representative group of patients with RA attending the KNH ROPC and explored the relationship between adherence disease activity and other patient characteristics. Socio-demographic trends indicate that the RA population in Kenya is getting older. The average age of patients in our study is 54.9 years which is in keeping with a trend of increasing patient age from a mean of 41.4 years in the year 2007, 48.7 years in 2016, 50 years in 2017 and 50.7 years in 2020[3,9,10,13]. This trend can have both a positive and negative connotation. It could indicate that RA patients are living longer due to better management of their disease hence being on follow-up for a longer time. On the other hand it could indicate that there is a delay in diagnosis of patients who are then predisposed to having more severe and advanced disease at treatment initiation.

The female to male ratio of our study population; 5.4:1, this more in keeping with global trends of 3:1 compared to previous findings in Kenya which showed a much higher female to male ratio of around 9:13 [9,10]. This change could be indicative of a shift toward increased health seeking behaviour among Kenyan men leading to a higher number being diagnosed with RA.

A higher proportion of patients was found to be rural dwelling than urban; 58.8%. This demographic characteristic has not been previously studied in our population hence we are unable to make a comparison. There was no significant difference in adherence to treatment between the two groups.

There was a trend toward significance (p= 0.11) when comparing single and married patients' levels of adherence with the former noted to be at a higher risk of non-adherence. This is in keeping with findings made in a systematic review of adherence to methotrexate therapy in RA whereby cohabitation was found to be a significant predictor of adherence [6].

A departure from previous local studies is the finding that there has been introduction of biologic DMARDs (5 patients) into the treatment repertoire with previous studies noting no usage of bDMARDs among study participants[3,9,10]. This is an encouraging finding given the low remission rates our population has demonstrated. However increased numbers would be needed to assess

the efficacy of these medications compared to the conventional DMARDS in attaining remission.

The level of adherence to DMARD therapy varies widely depending on many factors among them the tool used, patients' demographic and clinical characteristics. The most reliable indirect measure of adherence among patients with rheumatologic diseases remains the Compliance Questionnaire for Rheumatology-19 and we used an abbreviated and validated version of it; the CQR-5.

The total sample size obtained was 97 patients with 48 patients scoring higher than 16 out of 20 on the CQR-5 giving us an overall adherence rate of 49%. The mean CQR-5 score (SD) was 79.0% (70.5-87.5); an important benchmark to which future scores can be compared for a measurable assessment of improvement or reduction in the level of adherence.

Global averages for adherence are around the 66% mark[15] which puts our patient population at a much lower level of adherence. This was an expected finding given this population's historic tendency to have high disease activity[3,9,10,13]. While similar studies conducted in Africa are scarce to find, one carried out in Egypt demonstrated an adherence level of 65% [14].

While the adherence level found in our population was lower than global averages of 66% many studies have found even lower adherence levels. Prudente *et al*[8] found an adherence level of 16.4% in their sample of 55 Brazilian patients with rheumatoid arthritis. They found a duration of therapy longer than 15 years and the presence of more than six comorbidities to be associated negatively with adherence[8]. This indirectly coincides with our finding of patients who were on more than 6 drugs having a tendency toward non-adherence (p=0.184). This perhaps could be explained by the increased cost of drug acquisition and other difficulties associated with an increased pill burden.

Wabe *et al*[15] found a lower level of adherence at 27.3% among their sample of 110 patients with RA in Australia. This is much lower than that of our population (49.0%) however the median CQR score of 71-73% was comparable to that of our population's (79.0%). The only significant socio-demographic factor found to be associated with adherence was older age (>62 years). Similarly, we found a significantly higher level of adherence among patients younger than 62 years compared to those who were older (OR 2.62, 95% CI 1.07-6.45, p=0.033). This difference could perhaps be explained by this group of patients having a higher level of education than the older group with 54 patients having attained higher than primary education in the younger age group compared to three patients in the older age group[15].

Many studies, however, found a higher level of adherence. A study on 96 RA patients in France using the CQR-19 found an adherence level of 59%. All patients were on methotrexate with 57% also on biologic DMARDS. This is in stark contrast to our patient population where a minority were on bDMARDS (5.1%)[16].

A 2021 study on 88 rheumatoid arthritis patients carried out in Saudi Arabia using the CQR-5 found an adherence level of 84.1% [17]. In both the French and Saudi studies a pharmacist led counseling session was available, an amenity absent in our setting.

We used the CDAI to assess the level of disease activity. Studies undertaken at the same setting by Olago-Rakuomi *et al*[13], Ndirangu *et al*[10] and Jayant[13] found active disease in 97.0%, 90.4% and 97.2% respectively. While the number of patients in remission were few in those studies no patient in our study was in remission and while a conclusive answer is beyond the scope of our study it could be postulated that due to closure of the follow-up clinics due to Covid-19 safety protocols some patients may have fallen behind in their management. This factor may also have contributed to the overall low adherence level of our patients.

While no difference in adherence to DMARD therapy was found between groups with high and low disease activity, we did encounter a trend toward significance when comparing the mean CDAI score between the adherent and non-adherent groups (p-0.08). Perhaps with a larger sample size this difference may have been significant. This finding does indicate that poor adherence may be contributing to the high disease activity in our population of RA patients.

Conclusions

Adherence to DMARD therapy and disease activity among RA patients attending the KNH ROPC were determined using simple and effective tools. The adherence level was lower than global averages and WHO recommendations while disease activity was high. No significant association was found between adherence and patient factors. Closure of the clinics due to Covid-19 containment measures may have contributed to these findings. Enhanced patient follow-up, setting up of clinics in rural areas for improved accessibility and employment of rheumatology nurses may improve adherence.

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