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Original Article

The Impact of Pharmaceutical Care Services on Patients with Active Rheumatoid Arthritis: A Randomized Controlled Study

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ABSTRACT

The objective of our study was to investigate the impact of pharmaceutical care services on the detection and resolution of drug-related problems (DRPs) in rheumatoid arthritis (RA) patients. It was a randomized controlled study in which 60 eligible patients were recruited and randomly assigned to either an intervention (N = 30) or a control group (N = 30). The intervention group received pharmaceutical care services including management of drug-related problems (DRPs) in addition to standard care. Patients in the control group received only standard care. Both groups were evaluated for DRPs, disease activity, functional disability, adherence, quality of life, and laboratory tests that include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at baseline and after 6 months. After 6 months, a significant difference in DRPs, Morisky medication adherence scale (MMAS-8), number of adverse drug reactions, and administration errors were noted between the intervention and control groups. A significant reduction was observed in disease activity score 28 (DAS28), health assessment questionnaire (HAQ), RA quality of life (RAQoL) score, ESR, and CRP in the intervention group when compared to the control group. In conclusion, the introduction of pharmaceutical care services in RA patient treatment protocol effectively resulted in an improvement in the detection and prevention of drug-related problems. Moreover, these professional pharmaceutical practices showed a significant reduction in DAS28, HAQ, and RAQoL scores indicating a decrease in disease activity, and functional disability with an improvement in patient adherence and quality of life.

Keywords: *Rheumatoid arthritis; pharmaceutical care services; drug-related problems; adherence; quality of life.*

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disorder, although it always targets the synovium resulting in joint affection, yet it is a multisystemic disease and often leads to severe disability and increased risk of premature death **[1]**. The overall worldwide prevalence of RA has been estimated between 0.5% to 1% of adults from all ethnic groups **[2]**. Females are three times more likely to develop RA than males with a peak age of onset in the fifth decade of life **[3]**.

RA has a burden on both the individual and the society. Musculoskeletal deficits result in a drop in physical function, quality of life, and

cumulative comorbid risk **[4]**. Accordingly, a socioeconomic burden **[5]**.

Polypharmacy is common among patients with RA, their long treatment duration, chronic inflammatory status, and insufficient knowledge about the disease and treatment regimen increase their risk of developing DRPs **[6]**.

A drug-related problem (DRP), defined as a drug therapy problem, is any undesirable event experienced by a patient that involves, or is suspected to involve, drug therapy and that interferes with achieving the desired goals of therapy **[7]**. The categories of DRPs include drugs with no indication, the need for additional drug therapy, non-compliance to drug therapy, presence of the wrong drug, therapeutic duplication, adverse drug reactions (ADR), and administration errors.

In the implementation of pharmaceutical care services, the detection of DRPs is essential since they may interfere with the optimal desired patient outcome **[8]**. One of the most significant DRPs is poor medication adherence which can limit medication efficacy, lead to higher disease activity, lower quality of life, higher health care cost, and increase the prevalence of disability and mortality **[9, 10]**. Dietary interventions that are offered through pharmaceutical care services play an important role in the management of RA by reducing levels of inflammation, disease symptoms, disability, and disease progression **[11]**.

It was claimed that having clinical pharmacists on the wards with other medical personnel reduced the frequency of drug-drug interactions and increased patient knowledge of their medications, both of which led to a decline in the number of DRPs **[8]**.

Studies that were performed to assess the Egyptian rheumatoid arthritis patient's adherence to medications revealed poor adherence due to several reasons, the most important of which are little belief about medication due to lack of information and emotional factors, the complexity of regimens, low satisfaction with health care due to poor interaction of the physicians with their patients and the insufficient explanation of the benefits and side effects of the drugs **[12]**. Evidence evaluating the role of the clinical pharmacist in interventions to resolve DRPs and improvement of medication adherence for Egyptian RA patients is limited. Consequently, this study was designed to investigate the effect of applying pharmaceutical care services on RA patients' health status, adherence, and quality of life, as well as the detection, resolution, and prevention of DRPs in Ain Shams University (ASU) outpatient clinic RA patients.

2. Materials and Methods

2.1. Ethical Consideration

The study protocol was reviewed and accepted by the Research Ethics Committee for Experimental and Clinical Studies at the Faculty of Pharmacy, ASU, Cairo, Egypt (approval number: M.Sc No.156). The study was conducted according to the Declaration of Helsinki **[13]**. Written informed consent was signed by all the study participants. The study was registered at ClinicalTrials.gov and (NCT03743181) is the identifier.

2.2. Setting

The study was conducted at the rheumatology outpatient clinic, ASU hospitals, Cairo, Egypt.

2.3. Design

The study was a randomized controlled, parallel, open-label study performed on patients with active RA with a 6-months follow-up period, the study design flow chart was summarized in **Fig.1**.

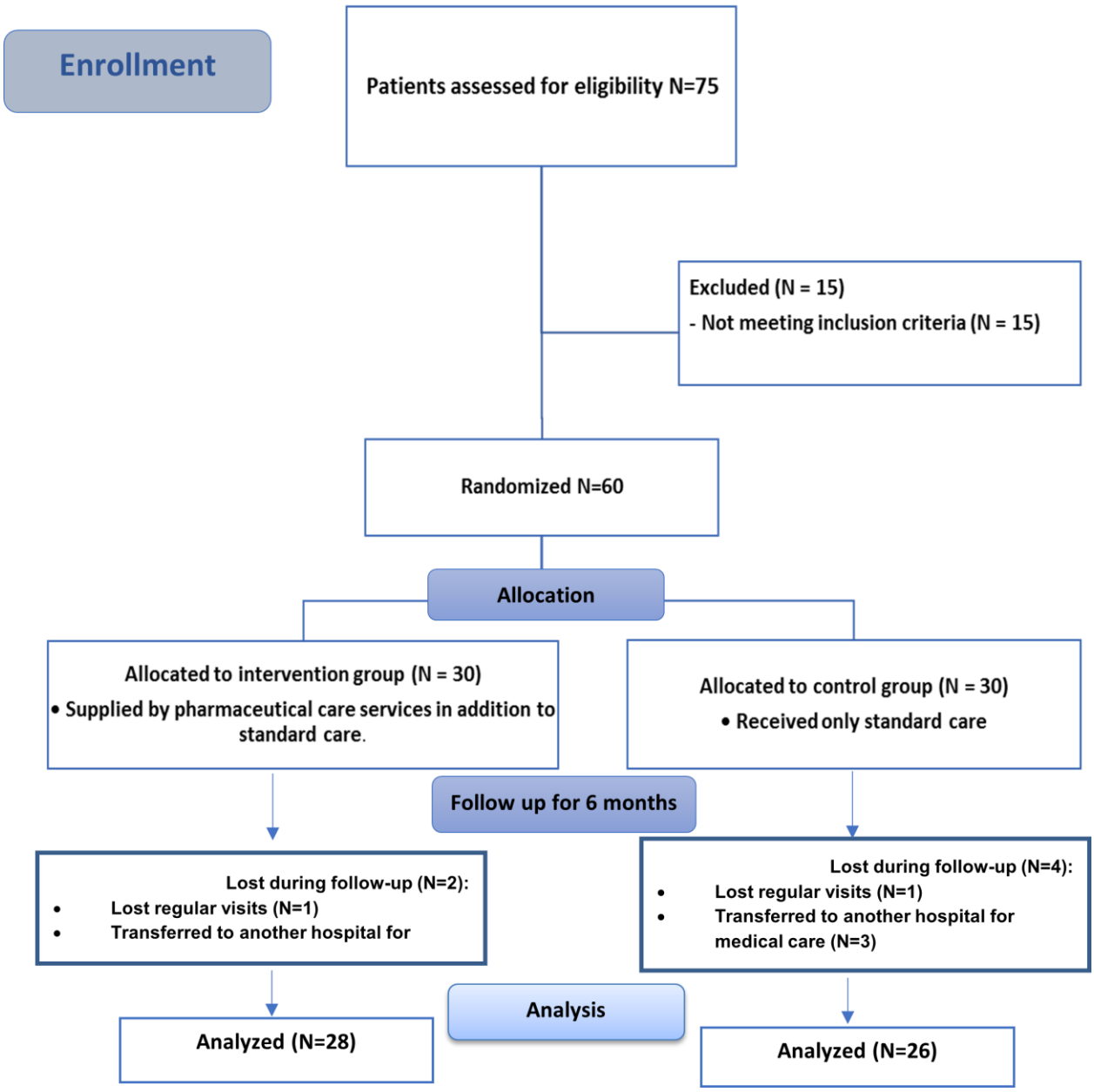

Fig. 1. Flow chart of the study

2.4. Patients

Sixty patients were randomly assigned by block randomization using the Sealed Envelope (London, UK) randomization tool **[14]** and allocated either to the intervention group (n=30) or the control group (n=30) based on the created randomization list with an allocation ratio of 1:1 and block size of 4.

Recruitment of subjects was performed according to the inclusion criteria which included: patients aged 18-60 years old, fulfillment of the American College of Rheumatology/European league against rheumatism (2010ACR/EULAR) diagnostic

criteria for RA, patients with active RA (defined by DAS28 score>2.6) **[15, 16]**. On the other hand, patients receiving biological therapy, those with cognitive impairment, hepatic or renal disease, other rheumatic and connective tissue disorders, also pregnant and nursing mothers were excluded.

2.5. Methods

Patients were divided into two groups, the control group which received standard care only, and the intervention group which received the pharmaceutical care services provided by the clinical pharmacist in addition to the standard care.

The standard care included physical examination of the patients and was performed by the attending physician, it comprised assessment of tender and swollen joints and any other health-related problems (such as hypertension, diabetes, dyslipidemia, hypothyroidism, hyperuricemia, and osteoporosis), the pharmaceutical care services were provided monthly for a period of 6-months through the patients' face to face interview. Four steps were involved in the pharmaceutical care process, these are presented in **Fig.2**.

During the study period, all patients were subjected to laboratory assessments that included fasting blood glucose (FBG) levels, lipid profile {total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)}, serum creatinine (SCr), complete blood count (CBC) with differential, alanine aminotransferase (ALT), aspartate aminotransferase (AST), ESR and CRP at baseline and the end of the study.

Participants were exposed to an assessment of disease activity, functional disability, adherence, and quality of life at baseline and at the end of the study using disease activity score28 (DAS28), a validated health assessment questionnaire (HAQ), 8-item Morisky medication adherence scale (MMAS-8) and validated Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire, respectively **[16-19]**. **Fig.3** represented the baseline data collected from the study participants at baseline and at the end of the study.

Patients' medications were checked and any differences in medications, doses, frequency, method of administration, additions/omissions, substitutions, or therapeutic duplicates were detected, and the reasons for these differences were discussed with the patient and recorded.

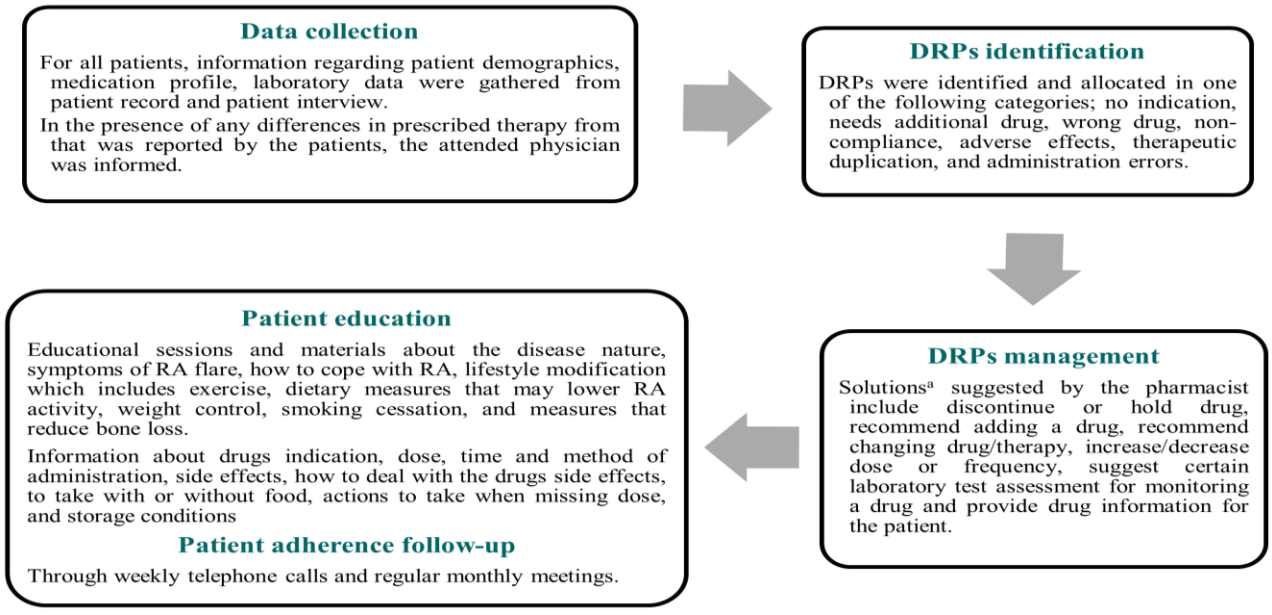

Fig. 2. Pharmaceutical care services chart showing detailed steps performed by the pharmacist. [a]All these solutions were based on suitable guidelines and discussed with the attending rheumatologist **[28]**. DRPs: drug-related problems

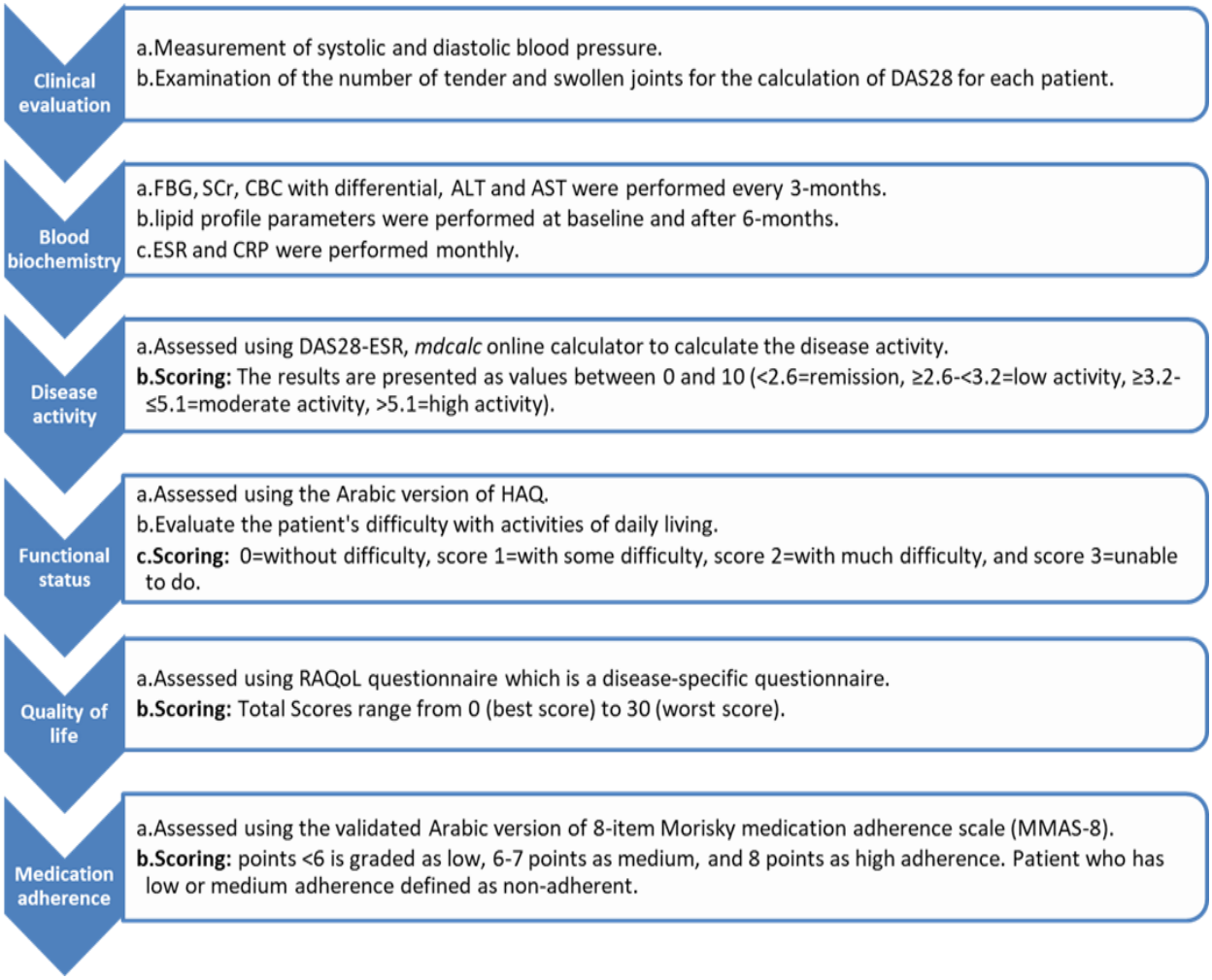

Fig. 3. Data collected from participants at baseline and at the end of the study

2.6. Primary and Secondary Outcomes

The primary outcome was the measurement of the change in the rate of incidence of DRPs through their detection and prevention applied procedures, the secondary outcomes were the changes in disease activity score28 (DAS28), patients' functional disability, and quality of life.

2.7. Statistical Analysis

Sample size calculation was performed using PASS program version 15, setting alpha error at 5% and power at 80% assuming a difference in the percentage of DRPs between the two study groups (intervention and control) that correspond to an effect size equal to 0.4 (effect size Ɠ) produced a sample of 30 cases per group taking into account a 20% drop rate.

IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA) was used for statistical analysis. The normality of the numerical data was tested using the Kolmogorov-Smirnov test and Shapiro-Wilk test and the results were expressed using the mean and standard deviation or median and range as appropriate. To express qualitative data, frequency and percentage were used. Pearson's Chi-square test or Fisher's exact test was used to comparing the qualitative variables between intervention and control groups. The mc-Nemar test or Sign test was used to compare qualitative

data before and after the intervention within each group.

Comparison between two groups was performed using either a student t-test for normally distributed data or the Mann-Whitney test for not normally distributed data. Paired t-test or Wilcoxon-signed ranks test was used to compare two consecutive measures of numerical data within each group. All tests were two-tailed. A p-value<0.05 was considered significant. Due to multiple comparisons, the p-value was corrected using the Bonferroni method.

3. Results

From January 2018 to December 2019 a total of 75 patients were assessed for eligibility, and only 60 patients fulfilled the inclusion criteria. Out of the 60 patients, 54 completed the study, 26 in the control group and 28 in the intervention group. The remaining six patients were dropped either because they failed to comply with the follow-up appointments (n = 2) or because their follow-up was transferred to another hospital (n = 4).

3.1. Patients' Demographics

Participants in both groups were comparable in all demographic characteristics. The mean age of participants was 44.67±9.7 years. The majority were married educated females with an average disease duration of 7.94±5.7 years. The most common comorbidities included hypertension, diabetes, osteoporosis, and asthma. Data regarding demographics were shown in **Table (1)**.

3.2. Clinical Characteristics and Laboratory Parameters of the Studied Groups

At baseline, there was no significant difference between the two groups regarding clinical characteristics and laboratory data, while at the end of the study the interventional group had significantly lower systolic blood pressure (SBP) than the control group (p=0.031). There was a significant reduction in ESR ($p\leq$ 0.001), CRP ($p\leq$ 0.001), total cholesterol ($p\leq$ 0.001), and LDL ($p\leq$ 0.001) in the interventional group compared to the control group as indicated in **Table (2)**.

3.3. Patients' Medications

Regarding patients' medications, they included the following: methotrexate (MTX) (75.92%) and hydroxychloroquine (HCQ) (87.03%) were the generally prescribed DMARDs, where MTX administration was reduced by 33.33% ($p=0.26$) in the intervention group at the end of the follow-up period. At the end of the study, there was a 33.33% (p=0.424) reduction in NSAIDs administration in the interventional group compared to an increase of 71.43% (p=0.125) in the control group, these changes did not reach statistical significance. On the other hand, glucocorticoid administration in the control group was significantly increased by 81.8% (p=0.016) at the end of the study. Moreover, in the intervention group, proton pump inhibitors/H2 receptor antagonists (PPI/H2RA) use was raised by about 28.57% (p=0.124) relative to the baseline data without any change in the control group. The percentages of the above-mentioned medications were presented in **Table (3)**.

3.4. Detection of Drug-related Problems

The findings shown in **Table (4)** demonstrated comparable information on the presence of DRPs between the groups under study at baseline. Nevertheless, compared to the control group as well as from baseline to the end of the trial period, the intervention group showed a significant improvement in compliance, a decrease in adverse drug reactions (ADRs), and a reduction in administration errors. **Fig.4** presented the number of patients who suffered from DRPs during the study period.

Table 1. Patients' demographics for the study groups

Variable	Control (n=26)	Intervention (n=28)	*p*-value
Age, years ± S.D.	46.2 ±9.2	43.2 ±10.2	0.260[a]
Gender (%)			N/A[e]
Male	0 (0.0%)	1 (3.6%)	
Female	26 (100%)	27 (96.4%)	
Disease history, years ± S.D.	8.7 ±5.3	7.9 ±6.1	0.252[d]
Education (%)			
Yes	16 (61.5%)	18 (64.3%)	0.835[b]
No	10 (38.5%)	10 (35.7%)	
Family history (%)			
Yes	12 (46.2%)	11 (39.3%)	0.610[b]
No	14 (53.8%)	17 (60.7%)	
Marital status (%)			
Single	1 (3.8%)	0 (0%)	N/A[e]
Married	23 (88.5%)	26 (92.9%)	
Widow	2 (7.7)	2 (7.1%)	
Presence of chronic diseases (%)			
DM	11 (42.3%)	10 (35.7%)	0.619[b]
HTN	14 (53.8%)	10 (35.7%)	0.180[b]
CHD	1 (3.8%)	3 (10.7%)	N/A[e]
Asthma	4 (15.4%)	4 (14.3%)	1.00[c]
Hypothyroidism	5 (19.2%)	2 (7.1%)	0.243[c]
Osteoporosis	5 (19.2%)	4 (14.3%)	0.724[c]
Hyperuricemia	2 (7.7%)	2 (7.1%)	N/A[e]

CHD, coronary heart disease; DM, diabetes mellitus; HTN, hypertension; S.D., standard deviation.

[a]independent T-test, [b]chi-square test, [c] Fisher's Exact test, [d]Mann-Whitney test, [e]N/A *p*-value is not available due to a small number of cases within subgroups, **p*-value is < 0.05; significant difference.

Table 2. Values of laboratory data for the study groups at baseline compared to the end of the study

Laboratory test (mean ± S.D.)	Baseline			End of study		
	Control (n=26)	Intervention (n=28)	*p*-value	Control (n=26)	Intervention (n=28)	*p*-value
ESR mm/hr.	62.3 ±21.7	59.9 ±20.1	0.710[d]	60 ±21.5	27.1 ±8.1	<0.001[d g *]
CRP mg/L	33.1 ±24.6	29.5 ±20.4	0.659[d]	24.6 ±21.3	6.6 ±4.8	<0.001[d g *]
Hb g/dL	12.3 ±1.3	11.8 ±1.7	0.205[a]	12.1 ±1.4	12.3 ±1.4	0.705[a]
WBC 10^3/uL	7.5 ±1.7	8.3 ±2.1	0.194[d]	7.9 ±1.2	8.0 ±1.8	0.903[d]
PLT 10^3/uL	336.2 ±100.2	287.9 ±62.9	0.111[d]	307 ±71.1	292.5 ±82.5	0.219[d]
TC mg/dL	204.5 ±37.8	192.7 ±27.8	0.146[d]	205.5 ±32	175.8 ±16.5	<0.001[d g *]
TG mg/dL	140.9 ±31.6	139.1 ±38.3	0.742[d]	134 ±22.7	128 ±27.1	0.337[d]
LDL mg/dL	126.9 ±39.4	118.7 ±24.2	0.180[d]	128.2 ±33.1	103.6 ±14.2	<0.001[d g *]
HDL mg/dL	49.4 ±6.7	46.2 ±8.1	0.081[d]	50.4 ±6.4	46.6 ±7.5	0.204[d g]
Creatinine mg/dL	0.84 ±0.18	0.73 ±0.13	0.060[a g]	0.81 ±0.17	0.78 ±0.17	0.564[a]
FBG mg/dL	112.4 ±30.7	117.1 ±41.8	0.986[a]	105.8 ±22.1	101.9 ±14.7	0.451[a]
AST IU/L	18.2 ±5.6	25.3 ±18.2	0.371[d]	26.8 ±20.2	19.1 ±5	0.869[d]
ALT IU/L	19.9 ±6.4	31.1 ±38.6	0.755[d]	28.1 ±20.6	17.5 ±6.8	0.084[d g]

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-Reactive protein; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PLT, platelets; S.D., standard deviation; TG, triglycerides; TC, Total cholesterol; WBC, white blood cells.

[a]independent T-test, [b]chi-square test, [c]Fisher's Exact test, [d]Mann-Whitney test, [e]N/A p-value is not available due to a small number of cases within subgroups, [f]N/A no statistics are computed as the number of patients in both groups was constant, [g]due to multiple comparisons, the *p*-value was corrected using Bonferroni method. **p*-value is < 0.05: significant difference.

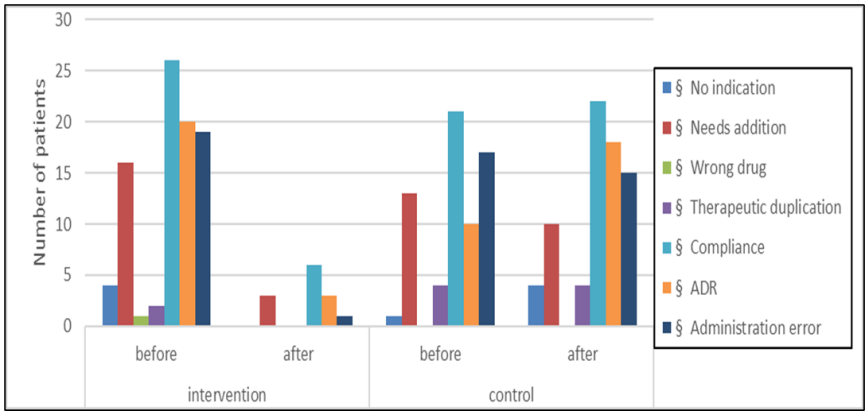

Fig. 4. Histograms showing the number of patients suffering from drug-related problems among the studied groups at baseline and after the end of the study

Table 3. Medications prescribed for the study patients at baseline compared to the end of the study

Medications consumption (%)	Baseline			End of study		
	Control (n=26)	Intervention (n=28)	*p*-value	Control (n=26)	Intervention (n=28)	*p*-value
MTX	20 (76.9%)	21 (75%)	0.869[b]	16 (61.5%)	14 (50%)	0.394[b]
HCQ	21 (80.8%)	26 (92.9%)	0.243[c]	22 (84.6%)	24 (85.7%)	1.00[c]
LEF	5 (19.2%)	7 (25%)	0.610[b]	11 (42.3%)	12 (42.9%)	0.967[b]
SSZ	1 (3.8%)	2 (7.1%)	N/A[e]	2 (7.7%)	5 (17.9%)	0.423[c]
Glucocorticoids	11 (42.3%)	21 (75%)	0.060[b g]	20 (76.9%)	21 (75%)	0.869[b]
NSAIDs	7 (26.9%)	12 (42.9%)	0.221[b]	12 (46.2%)	8 (28.6%)	0.181[b]
Folic acid	19 (73.1%)	21 (75%)	0.872[b]	15 (57.7%)	15 (53.6%)	0.761[b]
Calcium supplement	20 (76.9%)	25 (89.3%)	0.286[c]	21 (80.8%)	26 (92.9)	0.243[c]
PPI/H_2RA	21 (80.8%)	21 (75%)	0.610[b]	21 (80.8%)	27 (96.4%)	0.380[c g]

H_2RA, H_2Receptor antagonist; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAIDs, Non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SSZ, sulfasalazine.

[a]independent T-test, [b]chi-square test, [c] Fisher's Exact test, [d]Mann-Whitney test, [e]N/A *p*-value is not available due to a small number of cases within subgroups, [f]N/A no statistics are computed as the number of patients in both groups was constant, [g] due to multiple comparisons, the *p*-value was corrected using Bonferroni method. **p*-value is < 0.05: significant difference.

Table 4. Percent of detected drug-related problems among the studied groups at baseline compared to the end of the study period

Drug-related problems (%)	Baseline			End of study		
	Control (n=26)	Intervention (n=28)	*p*-value	Control (n=26)	Intervention (n=28)	*p*-value
No indication	1 (3.8)	4 (14.3%)	0.353[b]	4 (15.4%)	0 (0%)	N/A[c]
Required additional therapy	13 (50%)	16 (57.1%)	0.599[a]	10 (38.5%)	3 (10.7%)	0.068[a e]
Wrong drug	0 (0%)	1 (3.6%)	N/A[c]	0 (0%)	0 (0%)	N/A[d]
Therapeutic duplication	4 (15.4%)	2 (7.1%)	0.413[b]	4 (15.4%)	0 (0%)	N/A[c]
Compliance	21 (80.8%)	26 (92.9%)	0.243[b]	22 (84.6%)	6 (21.4%)	<0.001[ae*]
ADR	10 (38.5%)	20 (71.4%)	0.060[a e]	18 (69.2%)	3 (10.7%)	<0.001[ae*]
Administration error	17 (65.4%)	19 (67.9%)	0.847[a]	15 (57.7%)	1 (3.6%)	<0.001[ae*]

ADR, adverse drug reactions.

[a]chi-square test, [b]Fisher's Exact test, [c]N/A p-value is not available due to a small number of cases within subgroups, [d]N/A no statistics are computed as the number of patients in both groups was constant, [e]due to multiple comparisons, the *p*-value was corrected using Bonferroni method. **p*-value is < 0.05: significant difference.

3.5. Evaluation of Disease Activity, Functional Status, and Patient's Adherence

The baseline DAS28, Morisky adherence score, and HAQ statistical analysis results are presented in **Table (5)**, where a non-significant difference between the study groups is shown. However, as demonstrated in **Figs. 5 and 6**, there was a statistically significant difference between the two groups at the end of the study period.

Table 5. Results of the assessment of disease activity, medication adherence, functional disability, and quality of life among the studied groups at baseline compared to the end of the study period

Item	Baseline			End of study		
	Control (n=26)	**Intervention (n=28)**	***p*-value**	**Control (n=26)**	**Intervention (n=28)**	***p*-value**
DAS28 (%)			0.636[a]			N/A[d]
Remission	0 (0%)	0 (0%)		0 (0%)	3 (10.7%)	
Low	0 (0%)	0 (0%)		2 (7.7%)	8 (28.6%)	
Moderate	18 (69.2%)	21 (75%)		18 (69.2%)	17 (60.7%)	
High	8 (30.8%)	7 (25%)		6 (23.1%)	0 (0%)	
DAS28, ±S.D.	4.9 ±0.6	4.8 ±0.6	0.697[c]	4.6 ±0.8	3.2 ±0.5	<0.001[c*]
Adherence (%)			0.286[b]			<0.001[a e *]
Low	20 (76.9%)	25 (89.3%)		19 (73.1%)	2 (7.1%)	
Moderate	6 (23.1%)	3 (10.7%)		6 (23.1%)	14 (50%)	
high	0 (0%)	0 (0%)		1 (3.8%)	12 (42.9%)	
Adherence, ±S.D.	3.8 ±2	3.5 ±1.8	0.615[c]	4.7 ±1.9	7.2 ±0.9	<0.001[c*]
HAQ, ±S.D.	1.4 ±0.4	1.2 ±0.3	0.097[c]	1.3 ±0.4	0.7 ±0.3	<0.001[c*]
RAQoL, ±S.D.	16.6 ±2.9	16.3 ±4	0.807[c]	17 ±3.5	9.8 ±2.8	<0.001[c*]

DAS28, disease activity score 28; HAQ, Health assessment questionnaire; RAQoL, the Rheumatoid arthritis quality of life questionnaire; S.D., standard deviation.

[a]chi-square test, [b]Fisher's Exact test, [c]Mann-Whitney test, [d]N/A p-value is not available due to a small number of cases within subgroups, [e]due to multiple comparisons, the *p*-value was corrected using Bonferroni method. **p*-value is < 0.05: significant difference.

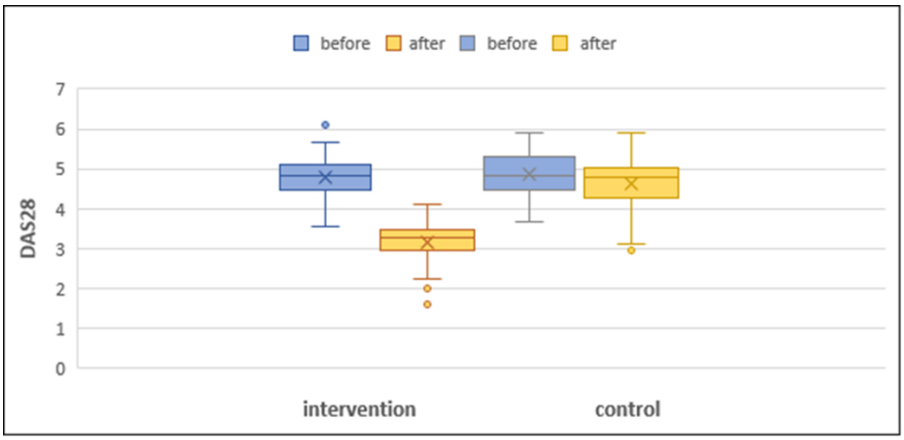

Fig. 5. Boxplot showing change in DAS28 score among the studied groups

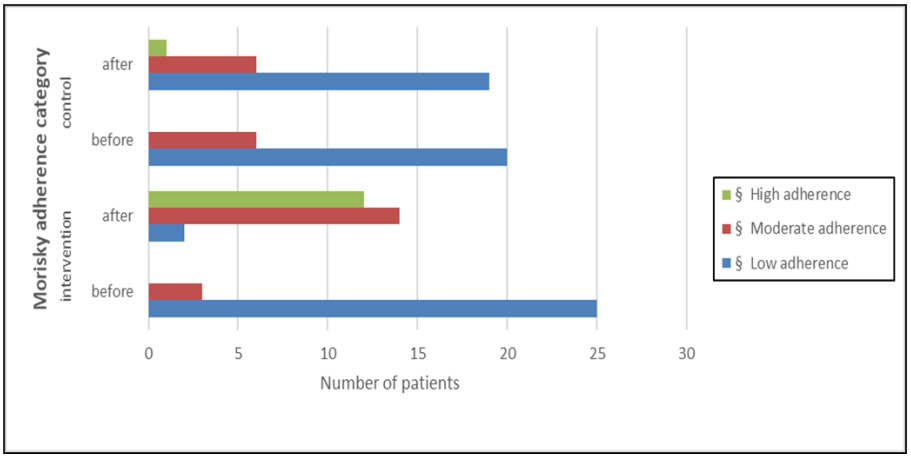

Fig. 6. Histograms showing the measured levels of adherence among the studied groups

4. Discussion

The present study aimed to evaluate the impact of pharmaceutical care services on DRPs, disease activity, and quality of life of RA patients.

The analysis of the study results revealed that after 6-months of providing pharmaceutical care services to RA patients along with the standard care provided by the rheumatologist, there was a significant improvement in DRPs (patient adherence to medications, ADRs, and administration errors), disease activity, functional disability, and quality of life in the intervention group when compared to the control group.

DRPs especially non-adherence and ADRs were reported in many studies performed on RA patients **[6, 12, 20]**. Non-adherence was the first most identified DRP in our study. We found that 83.33% and 16.67% of the total number of patients in the current study had low and moderate adherence, respectively, while no patients were with high adherence. These results approach those displayed by Gadallah et al. who reported that 90.6% of their Egyptian RA studied patients had low adherence to medications and 9.4% as moderate adherence and none was highly adherent to RA treatment **[12]**. Poor adherence by our patients may be linked to medication costs, lack of free drugs in the hospital pharmacy, and fear of side effects. Some patients discontinued their medications because they believed they were no longer effective due to the

absence of clinical improvement.

The significant improvement in patients' adherence at the end of the current study was reflected in the improvement in MMAS-8 in the intervention group compared to the control group and the number of patients suffering from non-adherence was decreased significantly in the intervention group, this was in agreement with the study by Taibanguay et al. who found that patients' education significantly improved adherence **[10]**.

In the present study, we dealt with the DRP of patient nonadherence through patient education by using educational material, conducting educational sessions, monthly appointments, and weekly call reminders were held which increased the patients' awareness about the importance of treatment in controlling symptoms and resulted in higher patients' compliance in the intervention than the control group.

The second most common DRP was adverse drug reactions with an incidence of 55% which differed from that reported by JE et al. in which a lower incidence of ADR in RA patients had been noticed **[21]**. A higher incidence of ADR at baseline in the current study population might be attributed to a lack of regular follow-up, and the presence of a large number of patients on the waiting list of the clinic making time available for each patient just enough for clinical examination and revising their medication. The lack of knowledge of patients about their medications and their side effects created an obstacle to reporting adverse effects that they have experienced. The major finding in the study accomplished by Pramote Tragulpiankit et al. was a high prevalence of ADR in RA and osteoarthritis ambulatory patients, one of their recommendations was that the cooperation with the pharmacist in the ambulatory patient care team could have helped to improve patient outcome through direct patient education and that what was done in our study **[22]**. The reduction in the incidence of ADR that was noticed in the intervention group at the end of the current study period might be attributed to the actions that have been taken by the pharmacist including symptomatic treatment, monitoring patients, and supplying patients with information about medication use and their side effects during the education process.

Administration error was the third most detected DRP in the current study, it was discovered that nineteen patients in the intervention group inappropriately administer their medications. The errors included incorrect administration methods, missed doses, and incorrect timing. The reasons behind this problem were a lack of understanding instruction for medication use from physicians and developing ADR from medications which led to patients missing doses or discontinuing treatment without informing the physicians. We tackled this problem by following up with the patients and educating them regarding their medication regimens and management of ADR.

In the current study, a statistically significant difference in disease activity was observed between the two study groups at the end. Similar results were reported by Ravindran and Jadhav and by Weimann et al., in which the groups that were subjected to educational services showed a significantly lower DAS28 score **[23, 24]**.

One of this study's objectives was to evaluate the effect of the provided pharmaceutical care services on the quality of life of RA patients and it was found that a significant improvement in HAQ was obtained in the intervention group. This finding was consistent with Senara et al. who found a significant difference between the two study groups regarding DAS28 and HAQ scores after conducting an educational program **[25]**.

A significant improvement evident by the lower mean of RAQoL in the intervention group compared to the control group at the end of the follow-up period was reported. This could be attributed to the decline in DRPs, improvement in disease activity, adherence, and patient education. In accordance with the aforementioned results, Intriago et al. demonstrated that the mean RAQoL was higher in patients with more disease activity and comorbidities (p<0.05) **[26]**. Moreover, Marra et al. estimated that an increase in the HAQ-DI score was associated with an increase in the RAQoL **[27]**. Accordingly, the implementation of pharmaceutical care services can highly contribute to the improvement of disease activity and consequently patients' quality of life.

Our study had several limitations. All participants have been recruited from the rheumatology clinic in a governmental hospital, so future multicenter studies should be carried out. Other limitations include the relatively small sample size, open-label nature of the study, and use of subjective self-reporting questionnaires.

Conclusion

From the current study, we concluded that the pharmaceutical care services provided to RA patients significantly decreased the incidence of DRPs. The patients' enhanced functional status and quality of life were both a result of these services, which also had a favorable effect on their overall health status as seen by an improvement in their disease state and adherence to their medication.

Recommendations

Since all participants have been recruited from a rheumatology clinic in a governmental hospital, future multicenter studies should be carried out. Nearly most of the study participants were females, thus, further studies including both sex are required.

Declarations

Ethics approval and consent to participate

The study protocol followed the ethical standards of the research ethical committee at the Faculty of Pharmacy, Ain shams university (approval number: M.Sc No.156) and performed in accordance with the principles and regulations of the Declaration of Helsinki. The study was registered at www. Clinical Trail.gov under registration No. NCT03743181. Informed consent was obtained from all patients before being participated in the study.

Consent to publish

Not applicable.

Availability of data and materials

All data generated and/or analyzed during the current study are involved in the published manuscript.

Competing interest

The authors declare that they have no conflict of interest.

Funding statement

No funding source was received.

Author contribution

Hagar Omar Elmenshawy, Marwa Adel Ahmed, Hanan Mohammed Farouk, and Nagwa Ali Sabri contributed to the conceptualization and methodology of the study as well as writing a review and editing of the final manuscript. Hagar Omar Elmenshawy was responsible for data collection, statistical analysis, and writing the original draft of the manuscript. Marwa Adel Ahmed, Hanan Mohammed Farouk, and Nagwa Ali Sabri were responsible for the supervision of all the study aspects. All authors contributed to the revision, reading, and approval of the submitted version of the manuscript.

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5. REFERENCES

1. Daniel Aletaha, T.N., Alan J Silman, Julia Funovits, David T Felson, et al., 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010.
2. Al-Bishri, J., et al., Comorbidity profile among patients with rheumatoid arthritis and the impact on prescriptions trend. Clin Med Insights Arthritis Musculoskelet Disord, 2013. 6: p. 11-8 DOI: 10.4137/CMAMD.S11481.
3. Tobon, G.J., P. Youinou, and A. Saraux, The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun, 2010. 35: p. 10-4 DOI: 10.1016/j.jaut.2009.12.009.
4. Kitas, G.D., and S.E. Gabriel, Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann Rheum Dis, 2011. 70(1): p. 8-14 DOI: 10.1136/ard.2010.142133.
5. Sokka, T., et al., Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther, 2010. 12(2): p. R42 DOI: 10.1186/ar2951.
6. Ma, S.N., H. Zaman Huri, and F. Yahya, Drug-related problems in patients with rheumatoid arthritis. Ther Clin Risk Manag, 2019. 15: p. 505-524 DOI: 10.2147/TCRM.S194921.
7. Al-Azzam, S.I., et al., Drug-related problems in a sample of outpatients with chronic diseases: a cross-sectional study from Jordan. Ther Clin Risk Manag, 2016. 12: p. 233-9 DOI: 10.2147/TCRM.S98165.
8. Abunahlah, N., et al., Drug-related problems identified by the clinical pharmacist at the Internal Medicine Ward in Turkey. Int J Clin Pharm, 2018. 40(2): p. 360-367 DOI: 10.1007/s11096-017-0585-5.
9. Zwikker, H.E., et al., Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: a randomized controlled trial. Patient Educ Couns, 2014. 94(3): p. 356-61 DOI: 10.1016/j.pec.2013.12.002.
10. Taibanguay, N., et al., Effect of patient education on medication adherence of patients with rheumatoid arthritis: a randomized controlled trial. Patient Prefer Adherence, 2019. 13: p. 119-129 DOI: 10.2147/PPA.S192008.
11. Khanna, S., K.S. Jaiswal, and B. Gupta, Managing Rheumatoid Arthritis with Dietary Interventions. Front Nutr, 2017. 4: p. 52 DOI: 10.3389/fnut.2017.00052.
12. Gadallah, M.A., et al., Assessment of rheumatoid arthritis patients' adherence to treatment. Am J Med Sci, 2015. 349(2): p. 151-6 DOI: 10.1097/MAJ.0000000000000376.
13. World Medical, A., World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA, 2013. 310(20): p. 2191-4 DOI: 10.1001/jama.2013.281053.
14. Sealed Envelope, L. Simple randomization service. 2021; Available from: [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/.
15. Villeneuve E, Nam J, and E. P, <2010 ACR-EULAR classification criteria for rheumatoid arthritis.>. Bras J Rheumatol, 2010. 50(5): p. 481-86.
16. Anderson, J., et al., Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken), 2012. 64(5): p. 640-7 DOI: 10.1002/acr.21649.

17. El Meidany, Y.M., M.M. El Gaafary, and I. Ahmed, Cross-cultural adaptation and validation of an Arabic Health Assessment Questionnaire for use in rheumatoid arthritis patients. Joint Bone Spine, 2003. 70(3): p. 195-202 DOI: 10.1016/s1297-319x(03)00004-6.

18. Jamous, R.M., et al., Adherence and satisfaction with oral hypoglycemic medications: a pilot study in Palestine. Int J Clin Pharm, 2011. 33(6): p. 942-8 DOI: 10.1007/s11096-011-9561-7.

19. de Jong, Z., et al., The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol, 1997. 36(8): p. 878-83 DOI: 10.1093/rheumatology/36.8.878.

20. Ernst, M.E., S.S. Iyer, and W.R. Doucette, Drug-related problems and quality of life in arthritis and low back pain sufferers. Value Health, 2003. 6(1): p. 51-8 DOI: 10.1046/j.1524-4733.2003.00202.x.

21. JE, M.-A., R. AF, and M.-D. ME, Adverse drug reactions associated with the use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. Rev Panam Salud Publica 2014. 36(6): p. 396–401.

22. Pramote TRAGULPIANKIT, et al., <Adverse drug events in rheumatoid arthritis and osteoarthritis ambulatory patients.pdf>. International Journal of Rheumatic Diseases 2012. 15: p. 315–321.

23. Ravindran, V. and R. Jadhav, The effect of rheumatoid arthritis disease education on adherence to medications and followup in Kerala, India. J Rheumatol, 2013. 40(8): p. 1460-1 DOI: 10.3899/jrheum.130350.

24. Weimann, C.A., et al., Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum, 2013. 65(6): p. 1421-9 DOI: 10.1002/art.37917.

25. Senara, S.H., W.Y. Abdel Wahed, and S.E. Mabrouk, Importance of patient education in the management of patients with rheumatoid arthritis: an intervention study. Egyptian Rheumatology and Rehabilitation, 2018. 46(1): p. 42-47 DOI: 10.4103/err.err_31_18.

26. Intriago, M., et al., Quality of life in Ecuadorian patients with established rheumatoid arthritis. Open Access Rheumatol, 2019. 11: p. 199-205 DOI: 10.2147/OARRR.S216975.

27. Marra, C.A., et al., A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med, 2005. 60(7): p. 1571-82 DOI: 10.1016/j.socscimed.2004.08.034.

28. Singh, J.A., et al., 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken), 2016. 68(1): p. 1-25 DOI: 10.1002/acr.22783.