ORIGINAL ARTICLES

Patterns of drug use and factors affecting adherence to medication in patients with rheumatoid arthritis: A prospective, observational, hospital- based study

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Abstract

Introduction: RA affecting ~ 1% of the world population, is associated with high level of non-adherence in clinical practice. The adherence to RA treatment therapy is affected by multiple factors. The present study evaluated the factors affecting adherence to medications among RA patients.

Methodology: The prospective study was conducted from April 2014 to March 2015. Male and female subjects, aged ≥18 years, and diagnosed with RA were included in the study. Demographic data, disease- and treatment-related data, adverse event profile and investigation data were obtained from all the participants. Adherence to medication of the subjects was measured using adherence questionnaire. All the subjects were followed up at one month and at the end of 6 months. McNemar's test was used to analyse the difference in adherence from baseline to follow up. All the statistical analyses were performed using SPSS statistical software, version 17.0.

Results: The study included 124 subjects, with a male to female ratio of 0.25:1, mean age of 45 years and RA duration of 5 years. Mono and combination drug therapies were used in 59.1% and 41.9% of the subjects respectively. Methotrexate was the most frequently used drug as a part of the regimen (82.3%). Among the subjects, 88 (71%) were found to be adherent. The comparison of various factors revealed significant difference only for the duration of RA (P 0.04).

Conclusion: The adherence to antirheumatic medications among RA patients remains moderate and factors such as rural residence and older age (>45 years) can be associated with good adherence to RA medication. The study also corroborates the previous literature evidence suggesting methotrexate as the commonly used drug for managing RA.

Keywords: RA, DMARDs, adherence, duration of RA

Introduction

Rheumatoid arthritis is a systemic inflammatory autoimmune disease characterized by arthritis and extra-articular involvement. The disease affecting around 1% of the world population, is associated with higher risk of morbidity.[1] The treatment of the disease remains challenging and is associated with high levels of non-adherence in clinical practice.[2] Around two decades ago, NSAIDs were the most commonly prescribed RA medication, and drugs like DMARDs and corticosteroids were sparingly used.[3] However, after 2002, the pattern in prescribing RA medication changed from NSAIDs to DMARDs.[4] Schmajuk *et al.* (2014) reported that the use of DMARDs among RA patients with established disease ranges from 73-100%, and the use of biologic DMARDs from 6%-41%.[5] Literature evidence from population-based surveys evaluating the pattern of drug use in RA suggests that the DMARDs use varies from 47-73%.[5]

Adherence to medication is explained as a strong thought for the need of the medicine.[6] The adherence to drug therapy can significantly improve the efficacy of the treatment regimen and lower healthcare cost. The adherence reported in RA patients ranges from 30-80%.[7] Data from Indian studies report non-adherence/non-compliance to antirheumatic drugs among 52% of the patients, and interrupted compliance among 6%.[2] Sharma *et al.* (2015) reported dissatisfaction to drug therapy

Table 1: Clinical and demographic details of the study subjects

Parameters	Values*
Gender (M/F)	25/9
Age (years)	44.91±12.608
Duration of RA (years)	5.01±5.656
Comorbidities	52 (41.9)
Hypertension	37 (29.8)
Diabetes	12 (9.7)
Hypothyroidism	17 (13.7)
Others	4 (3.4)
Median duration of comorbidities (years)	
Hypertension	5 (4.5)
Diabetes	3.5 (3.75)
Hypothyroidism	2 (2.5)
Complications of RA	
2° Sjogren	10 (8.1)
Vasculitis	2 (1.6)
Osteoporosis	3 (2.4)
Median duration of complications (years)	
2° Sjogren	0 (1)
Vasculitis	2 (2)
Osteoporosis	2 (2)

* data are represented as mean±SD and n(%)

as a significant factor contributing to non-adherence in RA patients.[2] The non-adherence noted among RA patients arises from patient-related factors such as socio-demographic factors, patient-perception; treatment-related factors such as type of drug, method of administration, duration of the treatment, complexity of the regimen and combination therapy; and disease-related factors such as the duration of disease, severity of disease, presence of comorbidities and functional disabilities.[8]

Literature evidence suggests that there is lack of clarity in the established factors that are strongly and consistently associated with non-adherence to RA medication.[7] Moreover, medication adherence in RA patients are influenced by several factors.[6] The present study was conducted to evaluate the patterns of usage of antirheumatic drugs and to determine the factors affecting adherence to medications among patients with RA.

Subjects and methodology

The prospective, observational study was conducted at the immunology outpatient department of a tertiary care hospital in South India, over a period of 12 months from April 2014 to March 2015. The study was approved by the institutional ethics committee and informed consent was obtained from all the subjects. The study included both male and female subjects, aged ≥18 years, diagnosed with RA. RA patients with severe mental and physical disabilities were excluded from the study.

Demographic data; disease and treatment-related data such as the time of diagnosis, associated comorbidities, family history of RA, presence of complications (osteoporosis, vasculitis, 2° Sjogren), duration of treatment, daily drug dosage, generic name of the drugs used, comorbid conditions and complications associated with RA; adverse event profile; and investigation data (complete blood count, total count, ESR, RF level, thyroid hormone levels, anti- CCP antibodies, liver and renal function tests) were obtained from all the participants. Data regarding the usage of complementary and alternative medicines were not collected. Data was collected through personal interview and from medical records of the subjects.

Adherence to medication of the subjects was measured using adherence questionnaire. The questions were

Table 2: Drug treatment data of the subjects

Drug class	Drug	n (%)
DMARDs	Methotrexate	102 (82.3)
	Sulfasalazine	10 (8.1)
	Leflunomide	12 (9.7)
Anti-malarial	Hydroxychloroquine	95 (76.5)
	Chloroquine	13 (10.5)
Biologicals	Etanercept	1 (0.8)
NSAIDs	Etoricoxib	70 (56.5)
	Etoricoxib paracetamol combination	26 (21.0)
	Paracetamol	20 (16.1)
	Diclofenac gel	2 (1.6)
Steroids	Methylprednisolone	17 (13.7)
	Prednisolone	16 (12.9)
	Hydroxycortisone	1 (0.8)
	Deflazacort	2 (1.6)
Antidiabetic medication	Metformin	4 (3.2)
	Glimepiride	2 (1.6)
	Gliclazide	1 (0.8)
Antihypertensive medications		
ARBS	Losartan	11 (8.9)
	Telmisartan	2 (1.6)
ACEI	Enalapril	2 (1.6)
CCBs	Amlodipine	13 (10.5)
Diuretics	Hydrochlorothiazide	5 (4.0)
Beta Blockers	Atenolol	6 (4.8)
Anti-thyroid medication	Levothyroxine	14 (11.3)

modified to suit the local socio-cultural scenario without altering the overall meaning. Scores such as '0' and '1' were assigned, when patient answered 'Yes' and 'No' respectively. The overall score ranged from 0-8 and a score of 0-5 was considered as poor adherence, 6-7 as moderate adherence and 8 as good adherence to the prescribed medicine. All the subjects were followed up at one month and at the end of 6 months.

Statistics

Baseline data (demographic, clinical and treatment) were subjected to descriptive statistical analysis and expressed as mean (±SD), median, frequencies and percentages. The MMAS scores are expressed as mean (±SD) with their 95% confidence Intervals (CI). Categorical variables were compared using chi-squared ($\chi 2$) tests. Comparison of continuous variables between groups was carried out using unpaired student's t-test. The significant variables in univariate analysis were entered into a stepwise multiple logistic regression model to identify the significant predictors of adherence to antirheumatic medications. Statistical significance was set at $P < 0.05$. McNemar's test was used to analyse the difference in adherence from baseline to follow up. All the statistical analyses were performed using SPSS statistical software, version 17.0.

Results

The prospective study recruited a total of 124 subjects with a male to female ratio of 0.25:1, and mean age of 44.91 ± 12.61. Among the subjects, 69.4% (n=86) represented urban population and 30.6% (n=38) the rural population. Smoking and alcohol consumption was noted in 3 (2.4%) and 6 (4.8%) subjects and the history of smoking was noted in 8.6% of the subjects. The clinical and demographic

Table 3: Adverse drug Reactions in RA patients

Event	n (%)	Implicated drug
Nausea	32 (25.8)	Methotrexate
Vomiting	33 (26.6)	Methotrexate
Stomatitis (mouth ulcers)	34 (27.4)	Methotrexate Steroids
Headache	6 (4.8)	Hydroxychloroquine
Rash	10 (8.1)	Hydroxychloroquine
Hair loss	53 (42.7)	Methotrexate
Fatigue	18 (14.5)	Methotrexate Hydroxychloroquine
Deranged liver function	17 (13.7)	Methotrexate
Deranged renal function	9 (7.3)	NSAIDs

details of the study subjects are provided in table 1. Family history of RA was noted in 20 (16.1%) subjects and 5.01 (±5.656) years was the mean duration of the disease. Around 52 (41.9%) subjects had at least one comorbid condition, and hypertension (29.8%) was the most frequent. RA-related complications were found in 12.1% subjects with secondary Sjogren's syndrome (8.1%) being the most common complication.

Mono and combination drug therapies were used by 59.1% and 41.9% of the subjects respectively. For subjects with disease flare, steroid was prescribed for a month and then the drug was tapered, depending on the disease improvement. Methotrexate was the most frequently used drug as a part of the regimen (82.3%). The most commonly used anti-malarial was hydroxychloroquine (76.5%), nonsteroidal anti-inflammatory drugs (NSAIDs) was etoricoxib (56.5%) and steroid was methylprednisolone (13.7%). The only biologicals used by the study subjects was etanercept (0.8%). Anti-diabetic medications such as gliclazide, metformin and glimepiride were used by 5.6% of the subjects. Anti-hypertensive medications were received by 31.4% of the study subjects, which included drugs such as ARBs, ACE-I, diuretics, beta blockers and CCBs; and 11.3% of the subjects were on anti-thyroidal drugs. Other drug prescriptions included statins, antiplatelet agents, vitamin D, anti-ulcerative agents (PPIs), antiemetics, antibiotics, SSRIs and TCAs, anticonvulsants and phosphodiesterase inhibitors (Table 2).

The most common adverse drug reactions reported by the subjects were stomatitis (27.4), vomiting (26.6), nausea (25.8%), and hair loss (42.7%). Renal and liver dysfunctions occurred in 7.3% and 13.7% of the subjects respectively. Adverse drug events (drug-wise) noted is tabulated in table 3.

Of the 124 subjects, 111 (89.5%) completed follow up at 1 month and 101 (81.5%) at 6 months. Thirteen subjects were declared lost to follow up at one month and 23 patients at six months. Among the subjects 43 (34.7%), 64 (57.7%) and 51 (50.5%) subjects at baseline, one month and at six months had a full score of 8. A score of 6-7 was noted for 32 (31.7%) subjects at six months and six patients had a score of 0, at one and six months. 101 (81.5%) subjects received good family support in the management of the illness.

Out of the 124 subjects, 88 (71%) were found to be adherent and 36 (29%) non-adherent. The comparison of variables such as age, gender, marital status, residence location, education, occupation, month family income, physical activity, smoking, alcohol consumption, tobacco use, disease duration, family history of RA, comorbidities and complications, at baseline revealed that only the mean duration of RA differed significantly among the groups (P = 0.04). Other variables did not show statistically significant difference among the groups (Table 4). Moreover, the comparison of adherence level at one month (P = 1.0) and six months (P= 0.754) with the baseline did not show statistically significant difference. Comparisons of adherence levels at 1 month and baseline, and between 6 months and baseline are given in table 5 and 6.

The multivariate binary logistic regression analysis revealed that subjects with younger age group (<45 years)

Table 4: Comparison of baseline variables between adherent and non-adherent groups

Variables	Class	Non-adherent* (n=36)	Adherent* (n=88)	P value
Gender	Male	8 (32.0)	17 (68.0)	**0.71**
	Female	28 (28.3)	71(71.7)	
Age		42.36 ± 14.35	45.95 ± 11.75	
	<45	21 (33.9)	41 (66.1)	**0.23**
	>45	15 (24.2)	47 (75.8)	
Marital status	Not married	7 (38.9)	11 (61.1)	**0.31**
	Married	29 (27.4)	77 (72.6)	
Residence	Rural	12 (31.6)	26 (68.4)	**0.67**
	Urban	24 (27.9)	62 (72.1)	
Education	Illiterate	7 (28.0)	18 (72.0)	**0.89**
	Literate	29 (29.3)	70 (70.7)	
Occupation	Unemployed	22 (26.5)	61 (73.5)	**0.37**
	Employed	14 (34.1)	27 (65.9)	
Monthly family income	< 8,000	2 (11.1)	16 (88.9)	**0.70**
	> 8,000	34 (32.1)	72 (67.9)	
Physical activity	Sedentary	34 (29.3)	82 (70.7)	**0.79**
	Moderate	2 (25.0)	6 (75.0)	
Smoking	Present	1 (33.3)	2 (66.7)	**0.86**
	Absent	35 (28.9)	86 (71.1)	
Alcohol	Present	0 (0.0)	6 (100)	**0.10**
	Absent	36 (30.5)	82 (69.5)	
Tobacco use	Present	12 (40.0)	18 (60.0)	**0.12**
	Absent	24 (25.5)	70 (74.5)	
Disease duration		3.42 ± 3.35	5.66 ± 6.26	**0.04**
Family history of RA	Present	6 (30.0)	14 (70.0)	**0.91**
	Absent	30 (28.8)	74 (71.2)	
Comorbidities	Present	12 (23.1)	40 (76.9)	**0.21**
	Absent	24 (33.3)	48 (66.7)	
Complications	Present	6 (42.9)	8 (57.1)	**0.22**
	Absent	30 (27.3)	80 (72.7)	

* data are represented as mean±SD and n(%)

Table 5: Comparison of adherence levels at 1 month and baseline*

Levels	At baseline n = 124 (%)	At 1 month follow up n = 111 (%)	P value
Adherent	88 (70.9)	84 (24.3)	1.000
Non-adherent	36 (29.1)	27 (75.7)	

* McNemar test was done

Table 6: Comparison of adherence levels at 6 months and baseline*

Levels	At baseline n = 124 (%)	At 6 month follow up n = 101 (%)	P value
Adherent	88 (70.9)	83 (82.2)	0.754
Non-adherent	36 (29.1)	18 (17.8)	

* McNemar test was done

Table 7: Factors affecting adherence after adjusting for significant variables

Variables	Adjusted odds ratio	95 % Confidence interval		P value
		Lower limit	Upper limit	
Age (<45 years)	1.08	1.01	1.15	0.035
Residence (rural)	0.22	0.05	0.96	0.044
Comorbidities	0.15	0.02	0.99	0.050
Disease duration	1.03	0.86	1.20	0.664
Use of CAM	0.43	0.04	4.02	0.459
Past CAM use	7.35	0.80	67.55	0.078

are non-adherent to medications (OR 1.08, 95% C.I [1.01, 1.15]) compared to subjects aged >45 years. Additionally, subjects living in the rural areas were found to be more adherent than subjects belonging to the urban areas (OR 0.22, 95% C.I [0.05, 0.96]) (Table 7).

Majority of the subjects reported forgetfulness (88%), no effect of medications (77%), self-decision to stop medication (77%), lack of knowledge of the disease and its complications (66%), disease improvement and stoppage (50%), switch to complementary alternative medicines (50%), lack of faith in the benefits of treatment (44%), poor caretaker-patient relationship (44%), polypharmacy (33%), adverse events (27%), cost of medication (16%) and non-availability of allopathic medications (11%) as the reasons for non-adherence at the 6 month follow up.

Discussion

The 2002 American College of Rheumatology (ACR) recommends the use of DMARDs in patients with active disease at the early stage of RA, ideally within the first three months of the disease, unless contraindicated.[9,10] Based on a systemic review involving 1287 studies, Schmajuk *et al.* (2014) observed that DMARD use reported by the RA cohorts and registries range from 73-100%.[5] The present study noted methotrexate as the most frequently used DMARD in 82% of the subjects, followed by hydroxychloroquine in 76.5%, leflunomide in 9.7% and sulfasalazine in 8%. Feldman et al. (2018) conducted a population-based cohort study on 77,999 RA patients who started on conventional or biologic DMARDs.[11] The study noted that 28332 patients were on methotrexate, followed by 27,157 on hydroxychloroquine, 6505 on sulfasalazine, 2773 on leflunomide and 19,381 on biologic DMARDs. Although, more antirheumatic drugs are being introduced into the drug market for the treatment of RA, poor patient adherence can significantly hinder the management of the disease.

Salt *et al.* (2011) based on a review of literature involving 35 studies reported an adherence range from 30%-107% for DMARDs among RA patients.[12] The survey conducted by Bianchi *et al.* (2015) on 1568 Italian RA patients treated with cDMARDs and biologics, observed non-adherence to cDMARDs in 39.2% (37.5% in subjects treated with cDMARDs alone and 40.5% in subjects treated with cDMARDs and biologics) of the subjects.[13] Ragab *et al.* (2016) studied Egyptian RA patients (83% females) and reported non-adherence to DMARDs among a higher proportion of the subjects (62.5%).[14] Likewise, Sharma *et al.* (2015) based on a cross-sectional descriptive observational study conducted on Indian women suffering from RA, reported non-adherence to anti-rheumatic medications in 52% of the subjects.[2] However, the present

prospective study noted non-adherence to antirheumatic medications only in 29% of the RA subjects.

Literature evidence suggests contradictory observations on the factors affecting non-adherence to anti-rheumatic medication. Sharma *et al.* (2015) noted that multifactorial reasons such as sedentary lifestyle, illiteracy, low income, rural residence, polypharmacy, non-corticosteroid prescription, concomitant treatment for comorbid condition, ignorance/lack of knowledge of the disease and its course, lack of motivation, lack of clinical remission of the disease and inability to prevent functional loss were significantly associated with the non-adherence to medication. Whereas, cost of treatment, fear of adverse drug reactions, adverse drug events and forgetfulness did not significantly affect the non-adherence to medications.[2] On the contrary, Binachi *et al.* (2015) reported non-adherence to RA medication in 50% of the subjects due to forgetfulness, 25% due to fear of side effects, 17% due to polypharmacy and 13.5% due to thought of feeling better.[13] The authors also noted that non-adherence was significantly higher (66.7%) among patients reporting high impact of cDMARDs on life, taking care by family members (44%), having occasional job (49%), rarely practising sports (43%), taking corticosteroid in combination (47%) and receiving help from family members (48%). Moreover, Ragab *et al.* (2016) reported that factors such as rural residence, lack of disease awareness and lack of belief in the efficacy of the medication as significant factors responsible for non-adherence to antirheumatic medication.[14] Additionally, Feldman *et al.* (2018) suggested that self-efficacy, patient-healthcare provider relationship, social support, patient belief about medication and age can affect the medication adherence.[11] Duration of RA was the only factor that was significantly lower in the non-adherent subjects, when compared to adherent subjects in the present study. Furthermore, variables such as gender, marital status, education, occupation, monthly family income, physical activity, smoking, alcohol consumption, tobacco use, family history of RA, comorbidities and complications, did not differ significantly among the groups. Substantiating the observation of Binachi *et al.* (2015), the present study also noted forgetfulness among 88% of the subjects, stoppage due to disease improvement among 50% of the subjects, polypharmacy among 33% of the subjects and adverse events among 27% of the non-adherent subjects. Other factors such as no effect of medications (77%), self-decision to stop medication (77%), lack of knowledge of the disease and its complications (66%), switch to complementary alternative medicines (50%), lack of faith in the benefits of treatment (44%), poor care taker-patient relationship (44%), cost of medication (16%) and non-availability of allopathic medications (11%) also contributed to the non-adherence to medication, in the present study subjects. However, Sharma *et al.* (2015) reported switch over to alternate treatment in only 12% of the women subjects.[2]

Joplin *et al.* (2015) suggested that poor understanding of the advantages of conventional biomedical treatment attributes to the usage of complementary or alternative medications, as they are thought to have minimal risk.[15] Additionally, low literacy impairs the ability to adhere to the regimen. The authors also observed employment, cognitive impairment and higher out-of-pocket costs as the factors contributing to the reduced adherence in RA patients.

The present study noted that subjects with older age (>45 years) and rural residence are significantly more adherent to RA medication compared to non-adherent subjects. Substantiating evidence was reported by Tuncay et al. (2007) based on a prospective study.[16] The authors reported that older age was associated with greater compliance. However, Wong *et al.* (2007) and Pascual-Ramos *et al.* (2009) reported older age as a significant factor contributing to drug discontinuation.[17, 18] Although Salt *et al.* (2011) observed age and rural residence as independent predictors of medical adherence.[19] Sharma *et al*. (2015) and Ragab *et al*. (2016) reported that rural residence is a good predictor of non-adherence to drug.[2, 14] Similarly, Xie et al. (2018) reported rural residency as an increased risk factor for non-adherence to RA medication.[20] But the present study noted contradictory observation.

The reason for poor adherence in younger patients can be attributed to the need of taking regular lifelong medication and discontinuation of treatment once the pain relives. Even though the patient education about the disease resulted in better adherence and greater patient knowledge, their impact on adherence typically decreased over time. This fact underscores the need of providing repeated and constant patient educational remainders by doctors or through materials to improve the good patient adherence to treatment.

In the present study, 81.5% of patients had good family support in the management of their illness. Strong family support is vital for the management of chronic conditions like RA. Patients who had lesser or no family support were

noted to be poorly adherent to medications. It is vital to educate not only the patients but also the families in the management of RA, as better family support can improve treatment outcomes.

The present study holds strengths such as optimal sample size and fair representation of the different section of the society. Furthermore, this is one among the few studies reported from India evaluating the prescription pattern of antirheumatic drugs and the factors influencing adherence to anti-rheumatic medications. The study was able to complete 82% of follow up at 6 months, which justifies a sample size calculation with 80% power. One of the major limitations of the study was not evaluating the drugs used by the patients.

The study entails the need for randomized controlled trials involving larger sample size with longer follow-up periods, directed at examining patient outcome to substantiate the observations. Moreover, it also emphasizes the need to explain the patients the importance of treatment adherence as a part of patient education.

Conclusion

The present study substantiates the literature evidence suggesting methotrexate as the most frequent DMARD in use. The study signifies that adherence to anti-rheumatic medications among RA patients remains moderate and factors such as rural residence and older age (>45 years) can be associated with good adherence to RA medication.

Competing interests

The authors declare that they have no competing interests.

Citation

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