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
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.\(^6\)

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

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**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) | 5 (4.5)     |
| Hypertension                        | 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(%)
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

| 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) |
|                    | Hydroxyxylisone                       | 1 (0.8) |
|                    | Deflazacort                           | 2 (1.6) |
| Antidiabetic       | Metformin                             | 4 (3.2) |
| medication         | Glimepiride                           | 2 (1.6) |
|                    | Gliclazide                            | 1 (0.8) |
| Antihypertensive   | Losartan                              | 11 (8.9) |
| medications        | Telmisartan                           | 2 (1.6) |
| ARBS               | Enalapril                             | 2 (1.6) |
| ACEI               | Amlodipine                            | 13 (10.5) |
| CCBs               | Hydrochlorothiazide                   | 5 (4.0) |
| Diuretics          | Atenolol                              | 6 (4.8) |
| Beta Blockers      | Levotiroxine                          | 14 (11.3) |

**Table 2: Drug treatment data of the subjects**
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)

| 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                      |

Table 3: Adverse drug Reactions in RA patients
### 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              | <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(%)
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.

### 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  |

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. 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%. 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. 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. 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. 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%). 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. 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. 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. 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 anti-rheumatic medication. 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. 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.

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. 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. 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. Although Salt et al. (2011) observed age and rural residence as independent predictors of medical adherence. Sharma et al. (2015) and Ragab et al. (2016) reported that rural residence is a good predictor of non-adherence to drug. Similarly, Xie et al. (2018) reported rural residency as an increased risk factor for non-adherence to RA medication. 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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