

FACTORS INFLUENCING ADHERENCE TO DISEASE MODIFYING ANTIRHEUMATIC DRUGS AND ITS EFFECTS ON DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENT

Farid Uddin Ahmed^{1*} Misbahus Saleheen² Mohammed Jashim Uddin³ Sujat Paul⁴

Abstract

Background: Non-adherence in patients with Rheumatoid Arthritis (RA) using Disease Modifying Antirheumatic Drugs (DMARDs) will not only affect the patient's disease activity, but also the rheumatologist's treatment decisions, and lead to higher health care costs. Poor adherence has been shown to be linked to different factors in different studies. There is paucity of study among the RA patients of Bangladesh in this issue. This study was conducted to evaluate the factors influencing adherence to DMARDs and its effects on disease activity in RA patient.

Materials and methods: It was a hospital based cross-sectional study. Total 107 diagnosed cases of RA, on DMARDs at least for 3 months were included from Rheumatology Clinics of Medicine and Physical Medicine Department of Chittagong Medical College Hospital (CMCH) from January 2018 to December 2018. Severity of RA was assessed by Disease Activity Score (DAS-28) while drug adherence was measured by Morisky Medication Adherence Scale-8 (MMAS-8) questionnaire. The Beliefs about Medicines Questionnaire (BMQ) was used to assess beliefs about the necessity of medication and concerns about it.

Results: Out of the 107 RA patients there was female predominance with a male to female ratio of 1:2.15 and mean age was 45.53±12.13 years with a range of 18-69 years. Non-adherence with DMARDs was found among 80.4% of cases. Non adherent patients had significantly higher disease

activity as measured by DAS-28. Except belief about medication no other socio-demographic and disease related factors were associated with adherence level. Higher adherence was associated with stronger perceptions of necessity of treatment and less concerns about treatment.

Conclusion: Frequency of low adherence among RA patients was high and patients with lower medication adherence tended to have higher disease activity. The strongest relation with adherence was found to be beliefs about the necessity of the medication and it is modifiable. This provides hope to improve adherence.

Key words

Rheumatoid Arthritis; Medication adherence; Disease activity.

Introduction

RA is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and in some cases, extra-articular involvement with a prevalence of approximately 1%^{1,2}. Incompletely controlled RA results in severe progressive joint damage, functional disability, morbidity, and increased mortality³. Drug therapy is the cornerstone of this disease management and it is likely that good adherence is required for the full benefit of therapy⁴. Current guidelines recommend treating the majority of RA patients with DMARDs within three months of diagnosis. When taken as prescribed, these medications can result in remission of the disease as evidenced by normal tests of inflammation, lack of joint pain and swelling, and lack of radiographic progression of the disease. Remission of the disease achieves the goals of therapies, which are to prevent damage to joints, maintain functional status, and decrease pain⁵. However, it is well established that DMARDs can take months to exhibit noticeable therapeutic benefits and can sometimes have unpleasant side effects that prompt patients to stop taking them⁶⁻⁸. Medication non-adherence is influenced by different factors. Only a few factors showed strong evidence of association while most of the factors either showed conflicting or no association in different

1. Assistant Professor of Community Medicine
Chittagong Medical College, Chattogram.
2. Medical Officer
Upazila Health Complex, Anowara, Chattogram.
3. Associate Professor of Medicine
Chittagong Medical College, Chattogram.
4. Professor of Medicine
Chittagong Medical College, Chattogram.

***Correspondence:** Dr. Farid Uddin Ahmed
E-mail: fuahmed_34@yahoo.com
Cell : 01727 78 97 00

Submitted on : 19.01.2020

Accepted on : 02.02.2020

studies⁹⁻¹². A recent meta-analysis of 96 peer-reviewed studies involving over 24 000 patients across 24 long-term conditions and 18 countries showed that non-adherence was related to patients beliefs about medicines, measured by the Beliefs about Medicines Questionnaire (BMQ)¹³. These studies indicated that there was often some disconnect between the patients and prescribers view of the medicine. Many patients doubted their personal need for the treatment or harbored concerns and these beliefs are associated with non-adherence¹³.

Cornerstone of management of RA in Bangladesh is the use of DMARDs. There are not many studies in the Bangladeshi literature that examine the factors that influence DMARDs adherence in RA and there are few reliable data regarding the prevalence of adherence problem among RA patients or the variables that influence adherence. Identifying the factors that are associated to DMARDs adherence would allow the development of strategies to improve treatment outcome. In this context, we conducted this study to determine the adherence level to DMARDs among the RA patients attending in CMCH and to identify the factors influencing adherence.

Materials and methods

This was a cross sectional observational study conducted at different Rheumatology Clinics of CMCH from January 2018 to December 2018. Ethical review committee of CMC approved the study. A total of 107 diagnosed patients with RA as per American College of Rheumatology 2010 criteria were included. All patients had been on DMARDs for at least three months. Patients had malignancy or any other chronic diseases like hypertension, diabetes, asthma, COPD, osteoarthritis, CLD, dementia or acute confusional state, pregnant and lactating women and those who refused to participate were excluded from the study. After informed consent a pre-tested questionnaire was completed by the researcher. Demographic and socioeconomic data were recorded. Disease activity on the current visit was calculated by DAS 28 which has four variables; tender joint count, swollen joint count, patient pain visual analogue scale and erythrocyte sedimentation rate. Concomitant non-steroidal anti-inflammatory drugs and steroids taken by patient were noted.

Adherence Measurement: MMAS-8 is a generic self-reported, medication-taking behavior scale

used for a wide variety of medical conditions¹⁴. It consists of eight items focusing on past medication use patterns with a scoring scheme of “Yes” = 1 and “No” = 0 for the first seven items except item number five in which the values “Yes” and “No” are reversed and for the last item a five-point Likert response is used with options “never”, “once in a while”, “sometimes”, “usually” and “always.” In this Likert scale, values ranging from 0 to 1 were given at a specified interval of 0.25 with “0” given for “never” and “1” given for “always”. The items are then summed to give a range of scores from low adherence to high adherence with a maximum score of 8. Adherent was labeled if the MMAS - 8 score was ≤ 2 and if the MMAS - 8 score was > 2 it was labeled as Non-adherent.

The Beliefs about Medicines Questionnaire: It is a self-administered questionnaire, which assesses cognitive representations of medication. It comprises 2 scales: the BMQ-Specific which assesses representations of medication prescribed for personal use and the BMQ-General which assesses beliefs about medicines in General¹³. This questionnaire consists of 2 parts:

- i) The BMQ-Specific : An 10-item questionnaire incorporates 2 subscales, the Specific-Necessity subscale assessing patients’ beliefs about the necessity of prescribed medication (e.g “My health, at present, depends on my medicines”, “my medicines protect me from becoming worse”) and the Specific-concern subscale which addresses their concerns regarding potential adverse outcomes from its use (e.g “I sometimes worry about the long-term effects of my medicines”, “These medicines give me unpleasant side effects”).
- ii) The BMQ-General : An 8-item questionnaire, which also comprises 2 subscales, the General-Harm and the General-Overuse subscale. The 4 item General-Harm subscale assessing patients’ general beliefs and concerns about potential harm of medicines and the degree to which they are perceived by the individual as being harmful (e.g “Medicines do more harm than good”, “All medicines are poisonous”) and the General-Overuse subscale which addresses patients’ considerations regarding certain aspects of medication overuse, such as healthcare providers’ over-investment of trust in medicines or over administration of medicines due to lack of time (e.g “Doctors use too many medicines”, “Doctors place too much trust

on medicines”). Respondents indicate their degree of agreement with each individual statement about medicines on a 5-point Likert scale, (1=strongly disagree to 5=strongly agree). Scores obtained for the individual items within each scale are summed to give a scale score with higher scores indicating stronger beliefs in the concepts represented by the scale. BMQ and MMAS-8 section of CRF were translated from its original English form to local language (Bengali) by following Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures¹⁵.

In addition, data on demographic and socio-economic variables were collected (For example age, sex, education level, numbers of children, children at home, marital status, employment status, race, place of residence) alongside.

SPSS 23 was used for data processing and analysis. Continuous variables were reported as means and standard deviation or as medians and Interquartile Ranges (IQR) according to their distributions. Between groups comparison for all continuous variables were done by Mann-Whitney U test as distribution was not normal except age, for which independent sample t test was used. Categorical variables were expressed as count and percentages and comparisons were done by Chi square test or Fisher exact test as appropriate. Correlation coefficient among adherence status and RA disease activity score was calculated. Multivariate analysis was performed to explore how a number of variables might jointly affect adherence behavior. All social demography and disease related variables were entered into a logistic regression model with the dichotomous adherence evaluated by the MMAS-8 as the dependent variable. Statistical significance was defined as $p < 0.05$ and confidence interval set at 95% level.

Results

The characteristics of the study population are shown in Table I. Mean age was 45.53 ± 12.13 years. Females were 68.2%. Over all non adherence rate was 80.4% (86/106) (Not shown in the figure). Age, gender, level of education, marital status, monthly family income, smoking behavior, duration of RA and current number of drugs was not significantly different between adherent and non adherent patients. However patients who fulfilled the criteria for non adherence had increased disease activity score DAS 28 (p value < 0.001).

Table I: Characteristics of the 107 patients with RA and their level of adherence.

Characteristics	Total (n=107)	Adherent (n=21)	Non-Adherent (n=86)	p value
Age (Years)	45.53±12.13	45.76±14.64	45.48±11.53	0.869
Sex				
Female	73 (68.2)	12 (57.1)	61 (70.9)	0.222
Male	34 (31.8)	9 (42.9)	25 (29.1)	
Residence				
Rural	45 (42.1)	5 (23.8)	40 (46.5)	0.006
Urban	62 (57.9)	16 (76.2)	46 (53.5)	
Education				
Illiterate	53 (49.5)	9 (42.9)	44 (51.2)	
Primary	15 (14.0)	1 (4.8)	14 (16.3)	0.236
SSC	33 (30.8)	10 (47.6)	23 (26.7)	
HSC & above	6 (5.6)	1 (4.8)	5 (5.8)	
Monthly family income				
BDT				
<10,000	32 (29.9)	4 (19.0)	28 (32.6)	
10,000-19999	56 (52.3)	11 (52.4)	45 (52.3)	0.253
≥20,000	19 (17.8)	6 (28.6)	13 (15.1)	
Marital status				
Single	20 (18.7)	3 (14.3)	17 (19.8)	0.723
Married	87 (81.3)	18 (85.7)	69 (80.2)	
Smoking behavior				
Never or former	94 (87.9)	18 (85.7)	76 (88.4)	0.738
Current smoker	13 (12.1)	3 (14.3)	10 (11.7)	
Disease duration (Years)	4 (2-7)	3.5 (2.0-5.1)	4 (2.0-8.0)	0.158
Treatment duration (Years)	3 (1-6)	2.5 (0.96-4.89)	3 (2.0-6.85)	0.338
No. of currently taking drugs	5 (4-6)	4 (4-5.25)	5 (4-6)	0.284
Tender joint count	6 (2-10)	0 (0-0.50)	7.5 (4-10)	<0.001
Swollen joint count	0 (0-4)	0 (0-0)	0 (0-4)	<0.001
DAS-28	4.51 (3.22-5.19)	2.10 (1.61-2.75)	4.67 (3.83-5.35)	<0.001

Data are presented either in frequency (Percentage) or mean \pm SD or median (IQR) as appropriate. Significant values are in bold face.

Reported answers to MMAS-8 are presented in Table II. Slightly more than three fourth (78.5%) of the participants reported that they sometimes forgot to take their medications, about half of the (51.4%) participants reported that they did not take their medications on at least one occasion in the 2 weeks before the interview, 89.7% of the participants reported taking all of their medications on the day before the interview.

Table II: Self reported medication adherence behavior of study participants as determined by the MMAS-8.

Item	Answered yes n (%)
Do you sometimes forget to take your pills?	84 (78.5%)
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	55 (51.4%)
Have you ever stopped taking your medicine without telling your doctor because you felt worse when you took it?	41 (38.3%)
When you travel or leave home, do you sometimes forget to bring along your medicine?	66 (61.7%)
Did you take all your medicine yesterday?	96 (89.7%)
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	57 (53.3%)
Taking medicine every day is a real problem for some people. Do you ever feel that it is difficult for you to continue your treatment?	73 (68.2%)
How often do you have difficulty remembering to take all your medicine?	
a. Never	19 (17.8%)
b. Once a while	53 (49.5%)
c. Sometimes	23 (21.5%)
d. Usually	11 (10.3%)
e. All the time	1 (0.9%)

MMAS-8: Morisky 8-item Medication Adherence Scale.

The majority of the participants endorsed the beliefs that, their current health depended on their medication and that, their medications kept them from getting worse. Concerns about medicines were also reported. Many participants indicated that they are worried about being obliged to take their medicines and about becoming too much dependent on their medications. Many patients endorsed the belief that physicians have too much trust in medicines and that most medicines are addictive. However, few patients endorsed beliefs that medications were harmful (Table III).

Table III: Percentage of respondents agreeing/strongly agreeing with Beliefs about Medicines Questionnaire (BMQ) statements.

BMQ items	Agreeing or strongly agreeing
BMQ-Specific	
Specific-Necessity (BMQ-SN)	
My health, at present, depends on my medicines	84 (78.5%)
My life would be impossible without my medicines	69 (64.5%)
Without my medicines I would be very ill	75 (70.1%)
My health in the future will depend on my medicines	63 (58.9%)
My medicine protect me from becoming worse.	83 (72.9%)
Specific-Concern (BMQ-SC)	
Having to take medicines worries me	62 (57.9%)
I sometimes worry about long-term effects of my medicines	49 (45.8%)
My medicines are a mystery to me	23 (21.5%)
My medicines disrupt my life	24 (22.4%)
I sometimes worry about becoming too dependent on my medicines.	60 (56.7%)
BMQ-General	
General-Overuse (BMQ-GO)	
Doctors use too many medicines	39 (36.4%)
Natural remedies are safer than medicines	48 (44.8%)
Doctors place too much trust on medicines	70 (65.4%)
If doctors had more time with patients they would prescribe fewer medicines.	69 (60.7%)
General-Harm (BMQ-GH)	
People who take medicines should stop their treatment for a while every now and again	21 (19.6%)
Most medicines are addictive	58 (54.2%)
Medicines do more harm than good	31 (28.9%)
All medicines are poisons.	43 (40.2%)

Analysis of belief scores using Mann-Whitney test showed that adherent participants had significantly higher specific-necessity belief, lower specific-concern belief and lower general-overuse belief and lower general-harm belief compared with non-adherent participants (Table IV). The overall specific-necessity score was higher than the concerns score.

Table IV: Association between BMQ score and DMARDs adherence among RA patients.

BMQ items	Adherence level to DMARDs		p value
	Adherent (n=21)	Non-adherent (n=86)	
Specific-Necessity	19 (18-20)	16 (14.5-17)	0.043
Specific-Concern	14 (14-16)	16 (15-18)	0.049
General-Overuse	11 (9-13)	13 (11-15)	0.044
General-Harm	12 (11-15)	15 (12-17)	0.048

Multivariate analysis with adjustment of all these factors showed that patients who had higher necessity beliefs had lower odds of being non adherent. On the other hand, patients who had higher concern beliefs had higher odds of being non adherent (Table V).

Table V: Independent factors associated with non-adherence using binary logistic regression analysis.

Variables	Odds ratio (95% C.I.)	p value
Age, <60 yrs vs. ≥ 60 yrs	0.89 (0.14-10.01)	0.891
Sex, Female vs. Male	0.35 (0.02-8.09)	0.778
Residence, Rural vs. Urban	0.56 (0.01-3.01)	0.089
Marital status, Single vs. Married	0.84 (0.14-2.1)	0.723
Education		
Illiterate vs. Primary	0.58 (0.01-12.1)	0.897
Illiterate vs. Secondary	0.43 (0.01-13.1)	0.567
Illiterate vs. HSC & above	0.38 (0.01-12.1)	0.245
Monthly family income, BDT		
<10,000 vs. 10000-19999	0.29 (0.06-1.38)	0.121
<10000 vs. ≥20000	0.06 (0.01-0.70)	0.024
Specific-Necessity score	0.79 (0.59-0.93)	0.046
Specific-Concern score	1.53 (1.10-2.13)	0.011
General-Overuse score	1.31(0.96-1.09)	0.088
General-Harm score	0.86 (0.67-1.01)	0.220

CI: Confidence Interval. Significant p values are in bold face.

In the present study disease activity was positively related with MMAS score (Correlation coefficient: 0.576, p value: <0.001). DAS-28 score increases (Indicating higher disease activity) as the MMAS-8 score increases (Indicating higher non-adherence) (Not shown in graphs/Tables).

Discussion

Nowadays, medication adherence is a major contributor to treatment outcomes for chronic health conditions. The objective of this cross sectional study was to investigate the medication adherence to DMARDs and the association of this with disease

activity among RA patients as well as to evaluate the factors related to non-adherence. One hundred seven RA patients attending the CMCH, the 2nd largest government tertiary care hospital in Bangladesh, were studied for this purpose.

Adherence rate to DMARDs of this study population was 19.6% as evaluated by MMAS-8 scale. We do not have local studies to show exact figures for adherence to DMARDs in our RA patients. However, inadequate medication adherence is common in clinical practice; especially in RA, and rates of adherence to DMARDs are highly variable, ranging from 30% to 107% for conventional DMARDs¹⁶. Small, heterogeneous samples in different studies, multiple indicators of medication adherence used may have contributed to the variable rates reported by these studies¹⁷. Moreover Pasma et al noticed that non-adherence proportions per DMARD also increased over time, and non-adherence proportions were highest for sulfasalazine¹⁸. In our study median disease duration was 4 years and it might be a cause of such low adherence rate to DMARDs.

Adherence is believed to be the main contributor to treatment outcome in many clinical settings¹⁹. Likewise, non-adherence to medications generally worsens outcomes of treatments, leading to increased risk of adverse medical events, more consultations with physicians, higher rates of hospitalization and increased health care costs²⁰. In our study, disease activity is positively related with drug non-adherence and it was highly significant (p value: <0.001). This was in agreement with a current systematic review and meta-analysis of seven studies involving 1,963 participants to investigate a relationship between medication adherence and disease activity in RA patients which suggested that RA patients with higher medication adherence tended to have lower disease activity²¹. Though, the results of the meta-analysis indicated that there was no significant difference between medication adherent and non-adherent patients in SJC, VAS and CRP and only a significant difference was observed between medication adherent and non-adherent groups in ESR was. In contrast to that study, in our RA patients all of the parameters to calculate DAS-28 were significantly lower in adherent group in comparison to non adherent group.

Out of the 107 RA patients there was female predominance with a male to female ratio of 1:2.15. Mean age was 45.53 ± 12.13 years. About half of the patients were illiterate. Most of them were married and had a median monthly family income was BDT 10000. These demographic and socio-economic distributions of RA patients are similar with local and regional studies^{22,23}.

In the current study, we failed to identify any association between drug adherence and demographic factors (Age, sex, place of residence), socio-economic factors (Education level, marital status, and smoking behavior) disease characteristics (Disease duration, number of drugs). Over the past 30 years, a substantial number of reports have been published about medication adherence. In most of these studies, emphasis was made on the relationship between demographic/clinical variables and adherence. However, it seems that most demographic and clinical variables had no or limited predictive ability to explain variations in adherence^{19,24}.

The other approach which successfully explained a great portion of medication non-adherence among patients with chronic diseases was behavioral models. Several studies have successfully shown good correlation between beliefs about medicines and medication adherence. In the current study, we also found correlation between belief about medicine and medication adherence as assessed by BMQ²¹. A relevant study in this issue concluded that increased awareness of the patient's beliefs about medicines is needed and that health care providers should encourage patients to express their views about medicines in order to stimulate concordance and adherence to medication²⁵. A study carried out in United States to examine the relationships between beliefs about medications, health literacy and self reported medication adherence concluded that patients who had negative beliefs about medications reported low medication adherence²⁶.

In our study, patients strongly endorsed beliefs that medications are necessary for their health, but also reported concerns about taking medications on a regular basis. Since 45.8% expressed concerns about long term effects of taking medications, it is important for health professionals to be

aware of these concerns and direct patients' education and intervention to minimize such concerns and consequently minimize non-adherence. Patients who take medications for chronic illness need to know that their medications are not addictive and that medication have an acceptable safety profile for long term use. A study investigated beliefs about medications held by people with RA found that age and level of formal education had a weak negative association with specific concern scores. The authors of the study concluded that most people with RA have positive beliefs about the necessity of their medication. However, levels of concern were high and associated with helplessness and non-adherence²⁷.

A meta analysis obtained by reviewing 94 studies regarding adherence related beliefs about medicines demonstrated that, the higher adherence was associated with stronger perceptions of necessity of treatment, and fewer concerns about treatment¹³. In our study, analysis showed significant association between adherence and specific necessity and specific concern. It was interesting to find that medication adherence was not associated with the number of medications used. This might emphasize the idea that it is not the number of medications that affects adherence, rather it is the belief that medicines are important for one's life which determines the level of adherence. Therefore, assessment of medication beliefs may be important for success of medication improvement strategies. Health care providers should address the patient's beliefs about medications in the hope of improving medication adherence.

Limitation

Caution should be exercised in generalizing our study's findings due to the use of purposive sample from one institution. The sample size used in our study was relatively small. Moreover, the cross sectional design of the study prevents conclusions about the causality of the associations we observed. For example, we cannot be sure whether concerns about medications lead to non-adherence or whether non-adherence leads to greater concerns.

Conclusion

The results of the present study indicate that non-adherence is a serious problem in the treatment of

RA and it is associated with higher disease activity. BMQ is a useful tool to identify psychological factors that are linked to non-adherence in patients with RA. Stronger belief in the necessity or concern of one's medications is significantly associated with high adherence and that assessment of medication belief is important in understanding adherence of chronic medication users. The BMQ may identify people at risk of poor adherence providing opportunities to improve adherence. Clinicians should ask about medication adherence during every consultation and should engage with individual patients to identify specific factors that may be responsible for poor adherence behavior.

Recommendation

Future studies should use the BMQ to screen patients to identify those who are at high risk of non-adherence and map their treatment plan accordingly.

Acknowledgments

It was a self funded study. The authors would like to thank all survey participants for their involvement, as well as the Physicians of the Rheumatology clinics of CMCH for their collaboration and cooperation.

Contribution of authors

FUA-Design, conception, data analysis, manuscript drafting and final approval.

MS-Conception, design, data collection and final approval.

SP-Interprition of data, critical revision and final approval.

MJU-Data analysis, critical revision and final approval.

Disclosure

All the authors declared no competing interest.

References

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. *The Lancet*. 2001; 358 (9285): 903–911.
2. Scott DL, Wolfe F, Huizinga TW J. Rheumatoid arthritis. *The Lancet*. 2010; 376 (9746): 1094–1108.
3. Elliott RA. Poor adherence to medication in adults with rheumatoid arthritis: Reasons and solutions. *Disease Management and Health Outcomes*. 2008; 16(1):13–29.
4. Wabe N, Wiese MD. Treating rheumatoid arthritis to target: Physician and patient adherence issues in contemporary rheumatoid arthritis therapy. *J Eval Clin Pract*. 2016; 23(3):486-449.

5. American College of Rheumatology. Prevalence Statistics. 2008.[Internet] Available frm: <https://www.rheumatology.org/Learning-Center/Statistics/Prevalence-Statistics>.

6. Park DC, Hertzog C, Leventhal H, Morrell RW, Leventhal E, Birchmore D et al. Medication adherence in rheumatoid arthritis patients: Older is wiser. *J Am Geriatr Soc*. 1999;47(2):172–183.

7. Goodacre LJ, Goodacre JA. Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease-modifying medication. *Rheumatology*. 2004; 43(5):583–586.

8. Young A. Current approached to drug treatment in rheumatoid arthritis. *Prescriber*. 2008; 19(12):19–28.

9. Curkendall S, Patel V, Gleeson M, Campbell R S, Zagari M, Dubois R. Compliance with biologic therapies for rheumatoid arthritis: Do patient out-of-pocket payments matter? *Arthritis Care and Research*. 2008;59(10):1519–1526.

10. Hovstadius B, Petersson G. Non-adherence to drug therapy and drug acquisition costs in a national population—a patient-based register study. *BMC Health Services Research*. 2011; 11(1):1–11.

11. Fallis B A, Dhalla I A, Klemensberg J, Bell C M. Primary medication non-adherence after discharge from a general internal medicine service. *PLoS ONE*. 2013;8(5): e61735.

12. Pasma A, Spijker AV, Hazes JMW, Busschbach JJV, Luime JJ. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: A systemic review. *Seminars in Arthritis and Rheumatism*. 2013;43(1):18-28.

13. Horne R, Chapman SCE, Parham R, Freeman N, Forbes A. Understanding Patients' Adherence-Related Beliefs about Medicines Prescribed for Long-Term Conditions: A Meta-Analytic Review of the Necessity-Concerns Framework. *PLoS ONE*. 2013; 8(12): e80633.

14. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med. Care*.1986; 24(1):67–74.

15. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)*. 2000; 15;25(24):3186-3191.

16. Salt E, Frazier SK. Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: A narrative review of the literature. *Orthop Nurs*. 2010;29(4):260–275.
17. Curtis JR, Bykerk VP, Aassi M, Schiff M. Adherence and persistence with methotrexate in rheumatoid arthritis: A systematic review. *J Rheumatol*. 2016;43(11):1997–2009.
18. Pasma A, Schenk CV, Timman R, Jan JV, Bart JF, Williminj H et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. *Arthritis Res Ther*. 2015;17(281):1-10.
19. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: A meta-analysis. 2002; 40(9):794–811.
20. Salaffi F, Carotti M, Di Carlo M, Farah S, Gutierrez M. Adherence to anti-tumor necrosis factor therapy administered subcutaneously and associated factors in patients with rheumatoid arthritis. *J Clin Rheumatol*. 2015;21(8):419–425.
21. Lin L, Yafei C, Rulan Y, Shengnan C, Qian Z, Haoyang C et al. Medication adherence has an impact on disease activity in rheumatoid arthritis: A systematic review and meta-analysis. *Patient Preference and Adherence*. 2017;11:1343–1356.
22. Arshad N, Ahmad NM, Saeed MA, Khan S, Batool S, Farman S. Adherence to Methotrexate therapy in Rheumatoid Arthritis. *Pak J Med Sci*. 2016;32(2):413-417.
23. Lohani MKH. Efficacy of Methotrexate in Combination with Antioxidant Vitamins (A, C & E) versus Methotrexate alone in the Treatment of Rheumatoid Arthritis. [Thesis, MD Internal Medicine. Chattogram Medical College Hospital. 2016.
24. Bart JF, Hanneke EZW, Cornelia HM. Medication Adherence in Patients with Rheumatoid Arthritis: A Critical Appraisal of the Existing Literature. *Expert Rev Clin Immunol*. 2012;8(4):337-351.
25. Mårdby AC, Akerlind I, Jörgensen T. Beliefs about medicines and self reported adherence among pharmacy clients. *Patient Educ Couns*. 2007;69(1-3):158-164.
26. Gatti ME, Jacobson KL, Gazmararian JA, Schmotzer B, Kripalani S. Relationships between beliefs about medications and adherence. *Am J Health Syst Pharm* 2009;66(7):657-664.
27. Neame R, Hammond A. Beliefs about medications: A questionnaire survey of people with rheumatoid arthritis. *Rheumatology (Oxford)*. 2005; 44(6):762-767.