## Original Research

# ADHERENCE TO METHOTREXATE IN IRAQI PATIENTS WITH RHEUMATOID ARTHRITIS : A CROSS–SECTIONAL STUDY

**Ali M. Kadhim Al-Tuma[1] & Nizar Abdulateef Jassim [2]**

*[1] Department of Internal Medicine ,College of Medicine, Karbala University , Karbala, Iraq*

*[2] Department of Internal Medicine,College of medicine , University of Baghdad , Baghdad, Iraq*

**Corresponding author: doctor88ali@gmail.com*

**ABSTRACT**

**Introduction:** Methotrexate (MTX) is the most widely used disease modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA). In RA, medication adherence is variable and sub-optimal. Poor adherence affects 20-70% of patients. Adherence to MTX is the key to attaining the goal of low disease activity or disease remission. The aim of the study is to determine adherence of RA patients to MTX when used as a monotherapy and when combined with anti-tumor necrosis factor (TNF) and to look for the factors that may positively and negatively affect adherence. **Methods:** An observational cross sectional study was conducted at Rheumatology Clinic/Baghdad Teaching Hospital over a period from January-June 2020. A total of 100 patients diagnosed with RA according to American College of Rheumatology (ACR) and European League against Rheumatism (EULAR), 2010 criteria are included. All were on MTX for more than 3 months. A questionnaire was used to collect information from them. **Results:** Young age, middle-high educational level and good socio-economic state increase the regular MTX intake and thus improve the adherence. Long duration of the disease and treatment, oral and combination therapy decrease the patients' adherence. **Conclusion:** Non-adherence to MTX is noted frequently in RA patients and variable factors tend to affect adherence. Multiple factors encourage or discourage the continuity of MTX intake, some are related to patients themselves while others are related to the course of the disease or MTX itself.

**Keywords**: Adherence, Non-adherence, Methotrexate , Rheumatoid Arthritis.

**Introduction:**

Rheumatoid Arthritis (RA) is a chronic, systemic, inflammatory disorder of joints and connective tissues (Jeffery, 2014). The primary site of involvement is the synovium of the joints which become inflamed and proliferate (Firestein, 2017). Extra-articular manifestations might accompany the joint disease such as eye involvement, rheumatoid nodules, cardiovascular and hematological changes (Angelotti et al., 2017). The exact cause of RA is still unknown, but it tends to be multi-factorial. Genetic and environmental factors (smoking, pollutants, and others) play important roles (Lin et al., 2016). The incidence of RA is estimated to be 1%, Females are more affected than males with a predisposition for more severe disease manifestations. The peak age of presentation is around 30-45 years old and its incidence increases with age (Silman, 2001 ; Feist and Burmester, 2013). The characteristic, typical presentations of RA are pain and swelling in the small joints of hands, wrists and feet and prolonged morning stiffness, often more than 1 hour (Odells, 2014). Patients are classified as having RA according to the 2010 American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) classification criteria as shown in figure 1. They are scored from 0 to 10, a patient with a score equal to 6 is classified under the name "definite RA" (Neogi et al., 2010).

| 2010 ACR/EULAR Criteria for RA Diagnosis | | |
|---|---|---|
| **A.** | **Joint involvement** | |
| | 1 large joint | 0 |
| | 2-10 large joints | 1 |
| | 1-3 small joints | 2 |
| | 4-10 small joints | 3 |
| | >10 joints (≥1 small joint) | 5 |
| **B.** | **Serology (≥1 test result needed)** | |
| | Negative RF and negative ACPA | 0 |
| | Low-positive RF or low-positive ACPA | 2 |
| | High-positive RF or high-positive ACPA | 3 |
| **C.** | **Acute-phase reactants (≥1 test result needed)** | |
| | Normal CRP and normal ESR | 0 |
| | Abnormal CRP or abnormal ESR | 1 |
| **D.** | **Duration of symptoms** | |
| | <6 wk | 0 |
| | ≥6 wk | 1 |
| **Definite diagnosis requires total score ≥6/10.** | | |

**Figure 1: ACR/ EULAR classification criteria of RA,2010 (Neogi et al., 2010).**

*RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, CRP: C reactive protein, ESR : Erythrocyte sedimentation rate.

Methotrexate is one of the most frequently used DMARDs for RA either as a monotherapy or combination therapy. Methotrexate when used as monotherapy, it may induce low disease activity in about 30% of patients. (Singh et al., 2015). The precise mechanisms of action are not understood completely, it seems to have both anti-inflammatory and immune-modulatory actions (Ranganathan and McLeod, 2006).

Insight to the molecular pathogenesis of RA, the need of using targeted diseases modifying anti-rheumatoid drugs (DMARDs) has increased significantly to get a state of low disease activity or disease remission(McInnes and Schett, 2007). Early intervention with these DMARDs prevents joint damage and improves long term functional outcomes (Escalas et al., 2012). According to ACR and EULAR treatment guidelines for RA, MTX is an anchor drug whether alone or in combination with conventional or biologic DMARDs (Curtis et al., 2016). As in all chronic diseases, compliance to therapy plays a vital role in treatment success. Adherence to MTX is the key to attaining the goal of disease remission or low disease activity. Non adherence (NA) is defined as poor implementation of a generally continued therapy for one reason or another. It has been reported that NA to MTX is considered a major challenge in the real-world treatment of RA patients (Salt et al., 2010). Various social and economic issues predispose to NA and adherence could be promoted by physician counselling. However, due to the lack of follow up studies among MTX non-adherent RA patients, it is difficult to precisely assume the possible factors which might affect patients' adherence (Müller et al., 2017). NA to treatment may impair the patient's health by a progressively severe joint damage, functional disability, poor health-related quality of life and higher disease morbidity and mortality (Rapoff and Pediatr, 2002). In addition, NA increases the unnecessary clinic appointments and diagnostic tests with increased usage of additional treatments' modalities with an ultimate result of increased treatment cost (De Achaval and Suarez-Almazor, 2010). So, the study aimed to explore the patient and drug-related aspects of methotrexate adherence and it was one of few studies that deal with the MTX adherence. It tried to investigate or evaluate the MTX adherence and the barrier to the adherence to be considered and discussed clearly with the patients before the start of therapy

**Methods:**

This study is an observational cross sectional study was conducted at Rheumatology Clinic in Baghdad Teaching Hospital over a period from January 2020 to June 2020. A total of 100 patients (male =30, female=70) diagnosed with RA according to ACR and EULAR, 2010 criteria were included. The sample size was calculated according to the prevalence of RA in the population. All had been on MTX for more than 3 months. Informed consent was taken from the patients and the study was done under the supervision of Scientific Council of the Iraqi Board for Medical Specializations in Partial Fulfilment of the Requirement for the

Degree of the Fellowship of the Iraqi Board for Medical Specialization in Rheumatology and Medical Rehabilitation.

**Inclusion Criteria:**

1. Patients with RA diagnosed according to ACR /EULAR 2010 criteria for more than 1year duration.
2. Taking MTX for more than 3 months.

**Exclusion Criteria:**

1.Patients with chronic diseases which necessitate chronic drug intake: HT, DM, asthma and epilepsy.

2.Patients with multi-drug usage (combination therapy with DMARDs other than anti-TNF e.g. hydroxychloroquine, prednisolone and sulfasalazine).

3. Patients with mental illness: dementia and memory loss.

A questionnaire was used to collect information from the patients and verbal consent was taken from them to be included in the study. Adherence questionnaires, the Medication Adherence Report Scale (MARS-5) and the Compliance-Questionnaire-Rheumatology (CQR) as well as a visual analogue scale (VAS) measuring MTX adherence, were administered to these patients as the following (De Cuyper et al., 2016). Demographic data; Age in years, sex, address, educational level (primary, secondary and tertiary), socio-economic state (according to the monthly income of the family). Duration of RA (years), duration of MTX intake (years), the current dose of MTX mg/week), mode of intake: oral or S.C/ I.M. Combined with anti-TNF or not (type, dose and duration). Disease activity at the time of visit according to clinical disease activity index (CDAI) score as shown in figure 2 and table 1 (mild when CDAI of 2.8-10, moderate from 10-22 and severe 22 and above) (Jeka et al., 2018).

.

| Joint | Left | | Right | |
|---|---|---|---|---|
| | Tender | Swollen | Tender | Swollen |
| Shoulder | | | | |
| Elbow | | | | |
| Wrist | | | | |
| MCP 1 | | | | |
| MCP 2 | | | | |
| MCP 3 | | | | |
| MCP 4 | | | | |
| MCP 5 | | | | |
| PIP 1 | | | | |
| PIP 2 | | | | |
| PIP 3 | | | | |
| PIP 4 | | | | |
| PIP 5 | | | | |
| Knee | | | | |
| Total | Tender: | | Swollen: | |

**Figure 2: Clinical disease activity index (CDAI) score (Jeka et al., 2018)**

**Table 1: Calculation scores of CDAI (Jeka et al., 2018).**

| Variable | Range | Value |
|---|---|---|
| **Tender joint score** | **(0-28)** | |
| **Swollen joint score** | **(0-28)** | |
| **Patient global score** | **(0-10)** | |
| **Provider global score** | **(0-10)** | |
| **Add the above values to calculate the CDAI score** | **(0-76)** | |

To calculate both the patient global assessment disease activity and provider global assessment disease activity, the doctor must consider all the ways that arthritis affects the patient, and ask the patient to rate how well he/she is doing on the following scale ranging from Very well 0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 - 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10 Very poor.

Adherence to MTX: when 2 or less of prescribed MTX doses are omitted in the previous 8 weeks. Non- adherence to MTX: when 3 or more doses are omitted in the previous 8 weeks. Possible reasons which encourage or discourage the patients to take the drug were discussed.

Data were analyzed statistically by IBM SPSS Statistics for Windows Version 24.0 (IBM Corp., Armonk. N. Y,. USA). In each group, either mean ± SD for continuous data or number and percentage for categorical data was calculated. An independent sample student t-test was used for comparing parameters between both groups. For categorical values, Chi- square was used. Only at a P-value ≤ 0.05 the differences between the values were considered as significant statistically.

**Results:**

Below are demographic characteristics of both groups. There was a significant statistical difference between both groups regarding age (the adherent group is younger with a mean of 48.4± 10.4 vs 54.3±10.7 years old), educational level, socio-economic state (in which the non-adherent patient exhibited both low educational and socio-economic levels respectively) at a significant p-value of less than 0.05.

**Table 2: Demographic data of the studied groups.**

| **Parameter** | **Adherent=58** | **Non-adherent=42** | **P-value** |
|---|---|---|---|
| **Age M±SD** | 48.4± 10.4 | 54.3 ±10.7 | 0.008* |
| **Sex** | | | |
| **Male** | 16 | 14 | 0.53 |
| **Female** | 42 | 28 | |
| **Educational level** | | | |
| **High** | 6 (10.3%) | 2 (4.76%) | 0.009* |
| **Medium** | 34 (58.6%) | 14 (33.3%) | |
| **Low** | 18 (31%) | 26 (61.9%) | |
| **Socio-economic state** | | | |
| **High** | 4 (6.89%) | 2 (4.76%) | 0.001* |
| **Middle** | 44 (75.8%) | 18 (42.85%) | |
| **Low** | 10 (17.2%) | 22 (52.3%) | |

Table 3 illustrates the medical history of the patients in both groups represented by the duration of RA, disease activity (depending upon CDAI score), duration of MTX treatment, the dose of MTX, mode of MTX intake (oral vs parenteral) and type, duration of treatment (mono vs combined). There was a significant difference between both groups regarding duration of RA ( the duration of RA is less in the adherent group with a mean 7.6±3.8 vs 12.0±6.3 years non-adherent one), duration of MTX treatment (being less in the adherent group 4.5±3.0 vs 7.3±5.8 years), mode of intake (37.9% of the adherent group were on oral

treatment and 62% on parenteral, while 76.19% of non-adherent group on oral and only 23.8% on parenteral treatment) and type of treatment ( 58.6% of adherent patients used MTX monotherapy and 41.37% used MTX in combination with anti-TNF in contrast to 28.5% and 71.42 respectively in the non-adherent group). While, the activity of the disease, dose of MTX and duration of combined therapy showed no significant difference between both groups with a p-value> 0.05.

**Table 3: Medical history of patients in both studied groups.**

| Parameter | Adherent, 58 | Non-adherent, 42 | P-value |
|---|---|---|---|
| **Duration of RA(years)** | 7.6 ±3.8 | 12.0± 6.3 | 0.0001* |
| **Disease activity** | | | |
| **Mild (2.8-10)** | 0 (0%) | 0 (0%) | 0.58 |
| **Moderate (10-22)** | 48 (82.75%) | 33 (78.57%) | |
| **Sever >22** | 10 (17.2%) | 9 (15.5%) | |
| **Duration of MTX (years)** | 4.5 ±3.0 | 7.3 ±5.8 | 0.02* |
| **Dose of MTX** | 15.9± 4.2 | 15.2± 4.7 | 0.44 |
| **Mode of MTX intake** | | | |
| **Oral** | 22 (37.9%) | 32 (76.19%) | 0.001* |
| **Parenteral** | 36 (62.06%) | 10 (23.80%) | |
| **Type of treatment** | | | |
| **Mono** | 34 (58.62%) | 12 (28.57%) | 0.003* |
| **Combined with ant- TNF** | 24 (41.37%) | 30 (71.42%) | |
| **Duration of combined (years)** | 3.7± 2.3 | 3.8± 2.4 | 0.90 |

Table 4 shows the likely reasons which encourage the patient to take the drug regularly and in turn improve adherence to MTX. Improvement of joint pain is at the top of the list 86.2%, followed by RA control 79.3%, improvement of quality of life 65.5%, fear from RA complications 44.8%, fear from RA morbidity & mortality 31% and the lowest reason is fear from disability 24%.

**Table 4: Possible reasons for increased adherence to MTX**

| Parameter | Total number | Percentage |
|---|---|---|
| **Pain improvement** | 50/58 | 86.20% |
| **Improve quality of life** | 38/58 | 65.51% |
| **Disease control** | 46/58 | 79.31% |
| **Fear from RA complications** | 26/58 | 44.82% |
| **Fear from handicap & disability** | 14/58 | 24.13% |
| **Fear from RA morbidity & mortality** | 18/58 | 31.03% |

While table 5 explains the major reasons which decrease the RA patient adherence to MTX. Starting from forgetfulness 61.9%, lack of awareness of its importance in disease control 57.1%, lack of availability and lack of awareness regarding its' long term intake 42.5%, lack of affordability and fear from SE 38.0%, peoples' negative advice 33.33%, lack of family support and intractable SE 23.8% and only 14.2% due to difficulty regarding the mode of intake. No one of the patients had a concept of MTX dependence in long term use.

**Table 5: Possible reasons for decreased adherence to MTX.**

| Parameter | Total number | Percentage |
|---|---|---|
| **Forgetfulness** | 26/42 | 61.9% |
| **Lack of affordability** | 16/42 | 38.09% |
| **Lack of availability** | 18/42 | 42.58% |
| **Fear from dependence** | 0/42 | 0% |
| **Fear from side effects** | 16/42 | 38.09% |
| **Peoples' negative advice** | 14/42 | 33.33% |
| **Lack of awareness of its importance in disease control** | 24/42 | 57.14% |
| **Lack of awareness regarding its long term intake** | 18/42 | 42.85% |
| **Lack of family support** | 10/42 | 23.80% |
| **Difficulty regarding the mode of intake: oral or parenteral** | 6/42 | 14.28% |
| **Intractable side effects: nausea, vomiting, stomatitis, oral ulcers, epigastric pain…etc.** | 10/42 | 23.80% |

**Discussion**

The current study showed that about 58% of patients with RA exhibited adherence to MTX which is consistent with the results of many studies; one large American Cohort study that included more than 14,000 RA patients and a prevalence study of 2662 RA patients who reported an adherence rate up to 65% (McInnes and Schett, 2007 ; Escalas et al., 2012 ). However, a higher adherence rate of 80% was registered by a longitudinal study conducted in Denmark which followed 941 patients with RA for 10 years (Curtis et al., 2016).

The adherent patients in this study were significantly younger, with middle educational and socio-economic levels in comparison to non-adherent who exhibited an older age and low both educational and socio-economic levels. Similar results were obtained by Arshad et al. in 2016 despite no significant differences among these parameters (Arshad et al., 2016).

For disease activity, disease duration, dose and duration of the MTX therapy, the study showed a significant difference between both groups. The duration of RA and MTX intake was longer in the non-adherent group while both disease activity and dose of MTX showed no significant difference. This means that with increasing the duration of both disease and treatment, drug adherence is decreased. With the exception of disease activity, this result is in some agreement with what was recognized by some studies in which the adherent patients had the more active disease (Müller et al., 2017 ; Rapoff and Pediatr, 2002).

For the route of administration, the study concluded that the adherent group were used the parenteral rout more than the oral route in contrast to the non-adherent group. Although, little data is available regarding the adherence and route of intake as most studies compared between oral and parenteral including drug safety, efficacy, disease response and tolerability but not adherence. It had been reported by some studies that parenteral intake is associated with higher bioavailability, bypassing the 1$^{st}$ pass hepatic metabolism, a reduced frequency and intensity of some GI side effects than oral MTX which may improve treatment compliance and reduce MTX discontinuation rates (De Achaval and Suarez-Almazor, 2010 ; De Cuyper et al., 2016 ; Grijalva et al., 2007). Other studies suggested that there was no difference in adherence between oral and parenteral MTX intake and increased adherence to oral intake was reported in certain RA patients; those who had phobia from the injection, elderly patients who didn't have caregivers, those with severe involvement and deformity of hand joints in which they could not use their hand to inject themselves (Harley et al., 2003).

Studying the type of therapy, mono or in combination with anti-tumor necrosis factor, the results showed that patients who used MTX alone showed more adherence than those who used MTX in combination with anti-tumor necrosis factor. Little data is available regarding the difference in patients' adherence to MTX alone or in combination with other biological agents. However, few studies were directly assessed the patients' adherence as most of them tried to assess treatment efficacy, toxicity, disease control, symptoms improvement, drugs' interaction and side effects (Pascual-Ramos et al., 2009 ; Hovstadius and Petersson, 2011 ; Kromann et al., 2015 ; Rutkowska-Sak et al., 2009). Some studies had been suggested that despite improvement in RA symptomatology, combination therapy might potentiate MTX side effects especially GI upset, liver toxicity, anemia and increasing the risk of recurrent infections (chest infection) which indirectly lead to treatment discontinuation and ultimately lead to non-adherence to combination therapy (Curtis et al., 2016 ; Boers et al., 1997).

For the factors which tend to affect patients' adherence, the study showed that the most important factors that encourage the patients to take the drug are; 86.2% due to improvement of joint pain and 79.3% and 65.5% due to disease control and improvement of quality of life respectively. Psychological factors are also seemed to be another candidate, 44.8% of adherent patients take the drug due to fear from RA complications, 31% fear from morbidity & mortality and 24% fear from disability. These results were in proximity with what was reported by a study which illustrated that more than 60% of adherent RA patients took the drug regularly due to improvement of pain, up to 30% due to improvement in quality of life and approximately 5% due to fear from disability and long term RA complications with a statistically significant difference (Salt et al., 2010).

For non-adherence group, there were many factors that affect adherence; some are related to the patients and others are related to the drug itself. The most common patients related causes of decreased patients' adherence were forgetting the drug in 61.9%, lack of awareness of its importance in disease control in 57.1%, lack of awareness regarding its long term intake in 42.5%, and fear from its side effects in 38.09% which could be related to age and patients' education.

While the main drug-related factors were lack of availability in 42.58%, lack of affordability in 38.09% (which might be attributed to the low socio-economic state, expensiveness and the drug is not available in local pharmacies), intractable side effects in 23.8%, and 14.2% due to difficulty in the mode of intake, especially parenteral intake.

Peoples' negative advice and lack of family support are not uncommon, it constituted about 33.33% and 23.08% of causes of non-adherent respectively. Fortunately, no one of the patients had a concept of MTX dependence in long term use. These were highly in agreement with the results of most of the studies had been done on MTX adherence in RA patients with some differences in the percentages (Salt et al., 2010 ; Calguneri et al., 1999 ; Mottonen et al., 1999 ; Keystone et al., 2010 ; Keystone et al., 2014 ; Breedveld et al., 2006 ).

**Limitations:** Patients' lost from follow up, MTX intake for less than 3 months, self-discontinuation of the drug and multi-drug usage.

**Conclusion:** Non-adherence to MTX is noted frequently in RA patients, Multiple factors encourage or discourage the continuity of MTX intake, some are related to patients themselves while others are related to the course of the disease or MTX itself.

**Recommendations:** Future researches are highly recommended to study the effect of non-adherence on patient health outcomes, to provide a good patient education and counseling by doctor which might promote patients' adherence.

**Conflicts of Interest**

The author declares no conflicts of interest.

**References**


- Angelotti, F., Parma, A., & Cafaro, G. (2017). One year in review; pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol., 35(3):368-78.
- Arshad, N., Ahmad, N.M., Saeed, M.A., Khan, S., Batool, S., & Farman, S. (2016). Adherence to Methotrexate therapy in Rheumatoid Arthritis. Pak J Med Sci.,32(2):413-17.
- Boers, M., Verhoeven, A., & Marusse, H. (1997). Randomized comparison of combined step-down prednisolone, methotrexate and suphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet.,350:309–18.
- Breedveld, F., Weisman, M., & Kavanaugh, A. (2006). A multi-center, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum.,54:26–37.
- Calguneri, M., Pay, S., & Caliskener, Z. (1999). Combination therapy versus mono-therapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheum.,17:699–704.
- Cannon, G.W., Mikuls, T.R., Hayden, C.L., Ying, J., Curtis, J.R., & Reimold, A.M. (2011). Merging Veterans Affairs rheumatoid arthritis registry and pharmacy data to assess methotrexate adherence and disease activity in clinical practice. Arthritis Care Res.,63(12):1680–90.
- Curtis, J.R., Bykerk,, V.P., Aassi, M., & Schiff, M. (2016). Adherence and Persistence with Methotrexate in Rheumatoid Arthritis: A Systematic Review. J Rheumatol.,43(11):1997-2009 .
- Curtis, J.R., Xie, F., Mackey, D. (2016). Patient's experience with subcutaneous and oral methotrexate for the treatment of rheumatoid arthritis. BMC Musculoskelet Disord.,17, 405.
- De Achaval, S, & Suarez-Almazor, M.E. (2010). Improving treatment adherence in patients with rheumatologic disease. J Musculoskelet Med., 27(10).
- De Cuyper, E., De Gucht, V., Maes, S., Van Camp, Y., & De Clerck, L.S. (2016). Determinants of methotrexate adherence in rheumatoid arthritis patients. Clin

Rheumatol.,35(5):1335-9.
- De Thurah, A., Norgaard, M., Johansen, M.B., & Stengaard-Pedersen, K. (2010). Methotrexate compliance among patients with rheumatoid arthritis: the influence of disease activity, disease duration, and co-morbidity in a 10-year longitudinal study. Scandinavian J Rheumatol.,39(3):197–205.
- Escalas, C., Dalichampt, M., Combe, B., Fautrel, B., Guillemin, F., Durieux, P., Dougados, M., & Ravaud, P. (2012). Effect of adherence to European treatment recommendations on early arthritis outcome: data from the ESPOIR cohort. Ann Rheum Dis., 71(11):1803-8.
- Feist, E., & Burmester. G.R.(2013). Rheumatoid arthritis-clinical features. In: Watts, R.A., Conaghan, P.G., Denton, C, et al, editors. Oxford textbook of Rheumatology. 4th ed. United Kingdom: Oxford university press.,858-63.
- Firestein, G.S. (2017). Etiology and Pathogenesis of Rheumatoid Arthritis. In: Firestein, G.S, Budd, R.C., Gabriel, S.G., McInnes, I.B., O'Dell, J.R. Kelley and Firestein's Textbook of Rheumatology, 10th edition. Elsevier, Inc., 69: 1115.
- Grijalva, C.G., Chung, C.P., Arbogast, P.G., Stein, C.M., Mitchel, E.F., & Griffin, M.R. (2007). Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Medical Care.,45(10Suppl 2): S66–76.
- Harley, C.R., Frytak, J.R., & Tandon, N. (2003). Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Managed Care.,9(6 Suppl): S136–43 .
- Hovstadius, B., & Petersson, G. (2011). Non-adherence to drug therapy and drug acquisition costs in a national population--a patient-based register study. BMC Health Services Res., 11:326.
- Jeffery, R.C. (2014). Clinical features of rheumatoid arthritis. Medicine (Baltimore)., 42: 231–6.
- Jeka, S., Dura, M., Zuchowski, P., Zwierko, B., & Waszczak-Jeka, M. (2018). The role of ultrasonography in the diagnostic criteria for rheumatoid arthritis and monitoring its therapeutic efficacy. Adv Clin Exp Med.
- Keystone, E., Genovese. M., & Klareskog, L. (2010). Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis., 69:1129–35.
- Keystone, E., Landewe, R,, Van Vollenhoven, R. (2014). Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. Ann Rheum Dis.,73:2094– 100.
- Kromann, C.B., Lage-Hansen. P.R., Koefoed, M., & Jemec, G.B. (2015). Does switching from oral to subcutaneous administration of methotrexate influence on patient reported gastro-intestinal adverse effects? J Dermatolog Treat.,26(2):188–90 .
- Lin, J., HE, Y., & Chen, J. (2016). Datasets of YY1 expression in rheumatoid arthritis patients. Data Brief,. 9: 1034-38.
- McInnes, I.B., & Schett, G. (2007). Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol.,7(6):429-42.
- Mottonen, T., Hannonsen, P., & Leiralalo-Repoo, M. (1999). Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomized trial. Lancet.,353:1568–73.
- Müller, S., Wilke, T., & Fuchs, A. (2017). Non-persistence and non-adherence to MTX therapy in patients with rheumatoid arthritis: a retrospective cohort study based on German RA patients. Patient Prefer Adherence.,11:1253-1264 .
- Neogi, T., Aletaha, D., & Silman, A.J. (2010). The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. Arthritis Rheum.,62(9):2582–91.
- Odells, J.R. (2016). Rheumatoid arthritis. In: Goldman L., Schafer A. Goldman-Cecil Medicine. 25th ed. Philadelphia, Pa.: Saunders Elsevier.,264:1755.
- Pascual-Ramos, V., Contreras-Yanez, I., Villa, A.R., Cabiedes, J., & Rull-Gabayet, M. (2009). Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease

activity and with disability. Arthritis Res Therapy.,11(1): R26.
- Ranganathan, P., & McLeod, H. (2006). Methotrexate pharmacogenetics: the first step toward individualized therapy in rheumatoid arthritis. Arthritis Rheum.,54:1366–77.
- Rapoff, M.A., & Pediatr, A.N. (2002). Assessing and enhancing adherence to medical regimens for juvenile rheumatoid arthritis., 31(6):373-9.
- Rutkowska-Sak, L., Rell-Bakalarska, M., & Lisowska, B. (2009). Oral vs. subcutaneous low-dose methotrexate treatment in reducing gastrointestinal side effects. Reumatologia.,47(4):207–11.
- Salt, E., & Frazier, S. (2010). Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a narrative review of the literature,.29(4):260-75.
- Silman, A.J. (2016). Rheumatoid arthritis, ed 4, St. Louis, 2001, Mosby Elsevier.
- Singh, J.A., Saag, K.G., & Bridges Jr, S.L. (2016). 2015. American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol.,68(1):1–26.