The Effects of Different Drugs Regimens in the Disease Activity Index and Uric Acid Levels of Sudanese Patients with Rheumatoid Arthritis.

Ala'a E.A.E Eltahir[1], Osama S. Abbadi[2].

[1] Assistant professor of clinical Immunology and allergies, AlNeelain Universityy, Khartoum, Sudan.
[2] Lecturer of biochemistry, Faculty of medicine, Omdurman Islamic University, Sudan.

Abstract.

Background: In Sudan, rheumatoid arthritis is treated by steroids and disease-modifying anti-rheumatic drugs (DMARDs). The typically used DMARDs include methotrexate, hydroxychloroquine (HCQ), sulfasalazine, and leflunomide.
Objective: In this study, authors assess the different drug regimens used in Sudan and their role in affecting the clinical disease activity index (CDAI) and serum uric acid (UA) of the patients.
Methodology: This was a comparative analytical case control study enrolling 192 participants, (96) rheumatoid patients as cases and (96) non- rheumatoid as controls. Clinical disease activity index (CDAI) was performed to the patients, and venous blood samples, analyzed by automated spectrometry, were taken to measure the two groups uric acid. Results were analyzed using Microsoft Excel 2013. T-test was performed to assess the difference between two numerical means, and Analysis of variance (Anova) was used to assess the difference between three means or more. For categorical data, Chi-square test was used.
Results: Only four patients were males (5%0) and the remaining 95% were females. Mean UA in males was 5.6 while in females it was 4.45, and the difference was significant (P=0.047).The difference between genders concerning the CDAI grading was insignificant (P=0.51). Lefulonodmide gave the highest rate of CDAI remission (67%) and the lowest serum UA mean (4.26.), while HCQ gave the least percent of severe-high CDAI score (20%). The last mentioned results were all statistically insignificant (P>0.05).
Conclusion: CDAI score was not correlated to specific drug regimen in Sudan. Further studies are needed to assess the drug regimens effect in CDAI levels in Sudan.

Key Words: Rheumatoid arthritis, Uric acid, CDAI, Sudanese, DMARDs.
Corresponding author: Ala'a E.A.E Eltahir

Introduction.

Inflammatory arthritis and extra-articular involvement are hallmarks of the systemic autoimmune illness rheumatoid arthritis (RA). It is a chronic inflammatory condition that predominantly affects synovial joints and has an unclear cause (1). It often begins in small peripheral joints, frequently symmetric, and proceeds to affect proximal joints if left untreated (1). Joint deterioration caused by cartilage and bone loss over time because of joint inflammation. Early RA is described as having symptoms that have been present for less than six months, while established RA is defined as having symptoms that have been present for more than six months (2).About 0.24% of world population have RA, and, until now, there is no known cure for this disease[ ]. First-line therapy, which consists of the

two classes of non-steroidal anti-inflammatory medications (NSAIDs) and corticosteroids, aims to reduce inflammation and alleviate pain (2). NSAIDs are fast-acting and include acetylsalicylate (Aspirin), naproxen, ibuprofen, and etodolac.NSAIDs actthroughthe inhibition of cyclooxygenase pathway,hindering prostagla- ndins, prostacyclin, and thromboxanes formation. Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA (2)

Today, the standard-second line- of care is early treatment with disease-modifying anti-rheumatic drugs (DMARDs). The drugs typically used in treating RA include methotrexate, hydroxychloroquine (HCQ), sulfasalazine, and leflunomide (1).

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotideuridine monophosphat pyrimidine (2). A study by Choe and Kim published in 2015 mentioned that leflunomide reduced serum uric acid concentrations through increased urinary excretion of uric acid, which might not reflect changes in disease activity status in RA. This implies that uric acid may not influence systemic inflammation in RA (2).

In Sudan, the commonly prescribed drug regimens are steroid alone,steroid with a combination with other drug (mainly a DMARD), HCQ, Methotrexate, and, recently Lefulonomide. The long-term effect of these drugs in disease progression and patients' activity still not reported in literature. In this study, authors meant to assess the different drug regimens used in Sudan and their role in affecting the clinical disease activity index CDAI of the patients. Serum uric acid also was measured, concerning different combination of drugs.

Materials and Methods.

This study was conducted at two referred outpatient (ROP) clinics at Khartoum-Sudan. Cases that met the1987 revised criteria of American college of rheumatology (ACR) for rheumatoid arthritis enrolled as cases and non-rheumatoid patients as control subjects. The patients' sample size was120 patients.100 patients had been enrolled in the study after 20 quit due to financial limitations. Only 96 patients continue because three samples were missed and one sample was distorted, then 96 control subjects matched according to age and sex with the 96 cases and the total number was 192 participants including (cases and controls). 2ml of venous blood sample was withdrawn from cases and control subjects under aseptic conditions. The sample underwent centrifugation and then analyzed and calculated by automated spectrometry at the central lab of Omdurman Military Hospital.

Clinical disease activity index (CDAI) to assess the disease activity that depends mainly on clinical presentation (symptoms and signs). A recoded pre tested questionnaire and a written consent for data collection filled from the participants by the

research doctor. The study results analyzed by Microsoft Excel 2013. Data were presented in the results section in tables and figures: Table 1 exhibits general descriptive data and the significance level as P value is considered significant at 0.05 or less. Figures represents mean levels of specific parameters with p value highlighted. T-test was performed when in need to assess the difference between two means, and Analysis of variance (Anova) was used to assess the difference between two means. For categorical data, Chi-square test was used to determine the P value.

Ethical clearance obtained from IRB of Sudan Medical Specialization Board.

Results.

General descriptive data:

In this study, 7% of the patients were in the age between 21 and 40, 52% were between 41 and 60, 33% were between 61 and 80, and 8% were above 80 years of age. Only four patients were males (5%0) and the remaining 95% were females. Mean UA in males was 5.6 while in females it was 4.45, and the difference was significant (P=0.047). The difference between genders concerning the CDAI grading was insignificant (P=0.51). Figure 1.

Nine patients were using Steroid alone, while 65 were using steroid with other drug combination. Four patients used methotrexate alone and four with combination. Four patients used to take Lefulonomide and 14 in combination with other drugs, and seven patient were receiving HCQ alone for RA management, one patient was on Sulphaslalzine. Considering Patients on Steroids only, none of the patients (0%) was on remission, three (33.4%) scored a low CDAI, one (11.1%) scored moderate, and five (55.6%) had a high CDAI. In the patients who use Steroid combined with other drugs, Six (9.2%) were on remission CDAI, 11(16.5%) had low CDAI, 31(47.7%) had moderate CDAI, and 17(26.2%) had high CDAI.

In the Patients group using HCQ, Three (30%) had CDAI remission, 1(10%) scored low CDAI, 4(40%) had a moderate CDAI, and two (20%) were with a high CDAI.

In the patients group that uses Methotrexate, One (12.5%) had remission, 3(37.5%) scored a low CDAI, 1(12.5%) had a moderate CDAI and three (37.5%) were with a high CDAI.

In patients group using Lefulonomide only, two patients (67%) were on remission, and one (33%) has a high CDAI, and in the Lefulonomide using group in combination with steroid, one patient (6%) was on remission while eight (50%) had a high CDAI. There were five (31%) having a moderate CDAI, and two (13%) with a low CDAI. However, the P value of the difference between groups in CDAI grade was insignificant (P=0.1).

Different drug regimen and their effects in serum Uric Acid: Mean Serum UA in the patient using Lefulonomide was the lowest compared with other groups: 4.26±1.5mg/dl. UA was 4.54±1.17 mg/dl in the steroid using patients, 4.74±1.11mg/dl in the patient using methotrexate, and 4.6±1.7 mg/dl for patient on HCQ, and the overall mean UA was 4.51±1.26 mg/dl. The result, however, was statistically insignificant (P=0.58); table 1.

The differences between UA levels in the groups: steroid alone and in combinations, Methotrxate alone and in combination, and Lefulonomide alone and in combination, was not significant (P values=0.91; 0.84, and 0.33, respectively). Figure (3).

Table 1: Descriptive statistics of serum UA overall and in the different patients 'groups.

Variable/UA	*Overall*	*Steroids*	*Meth.*	*HCQ*	*Lef.*
Mean	4.51	4.54	4.74	4.6	4.26
Median	4.35	4.4	4.45	4.9	3.5
Mode	3.3	3.3	#N/A	N/A	3.5
Standard Deviation	1.260867	1.169179	1.110904	1.731088	1.541938
Range	5.1	5.1	3.1	4.8	4.8
Minimum	2.6	2.6	3.6	2.6	2.6
Maximum	7.7	7.7	6.7	7.4	7.4
Count	96	63	8	7	17
Confidence Level (95.0%)	0.255475	0.294454	0.928739	1.60099	0.792791
P value of the difference			0.58		

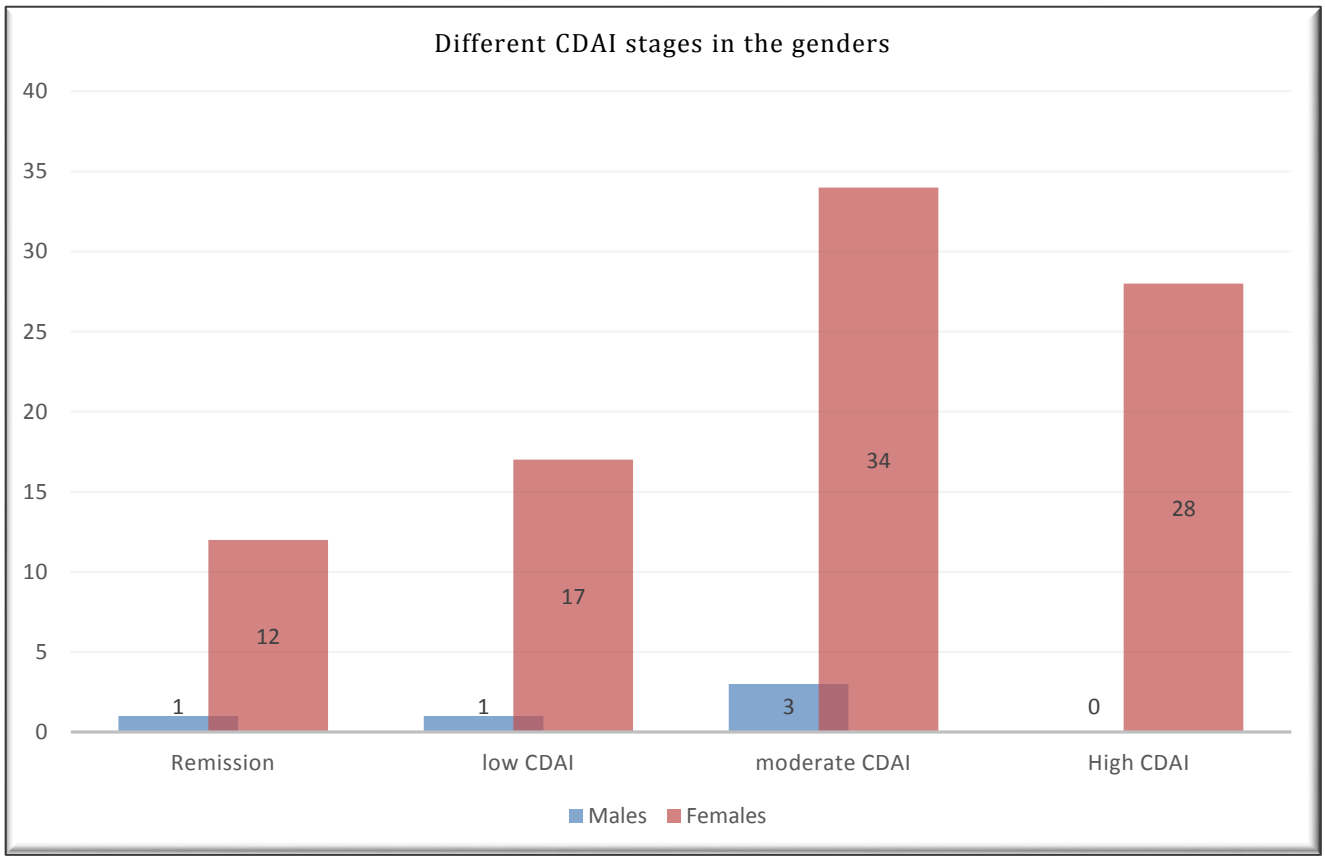

Figure 1: Difference in CDAI scores between male and female patients (P=0.047).

 DOI: 10.52981/smlj.v10i2.2843

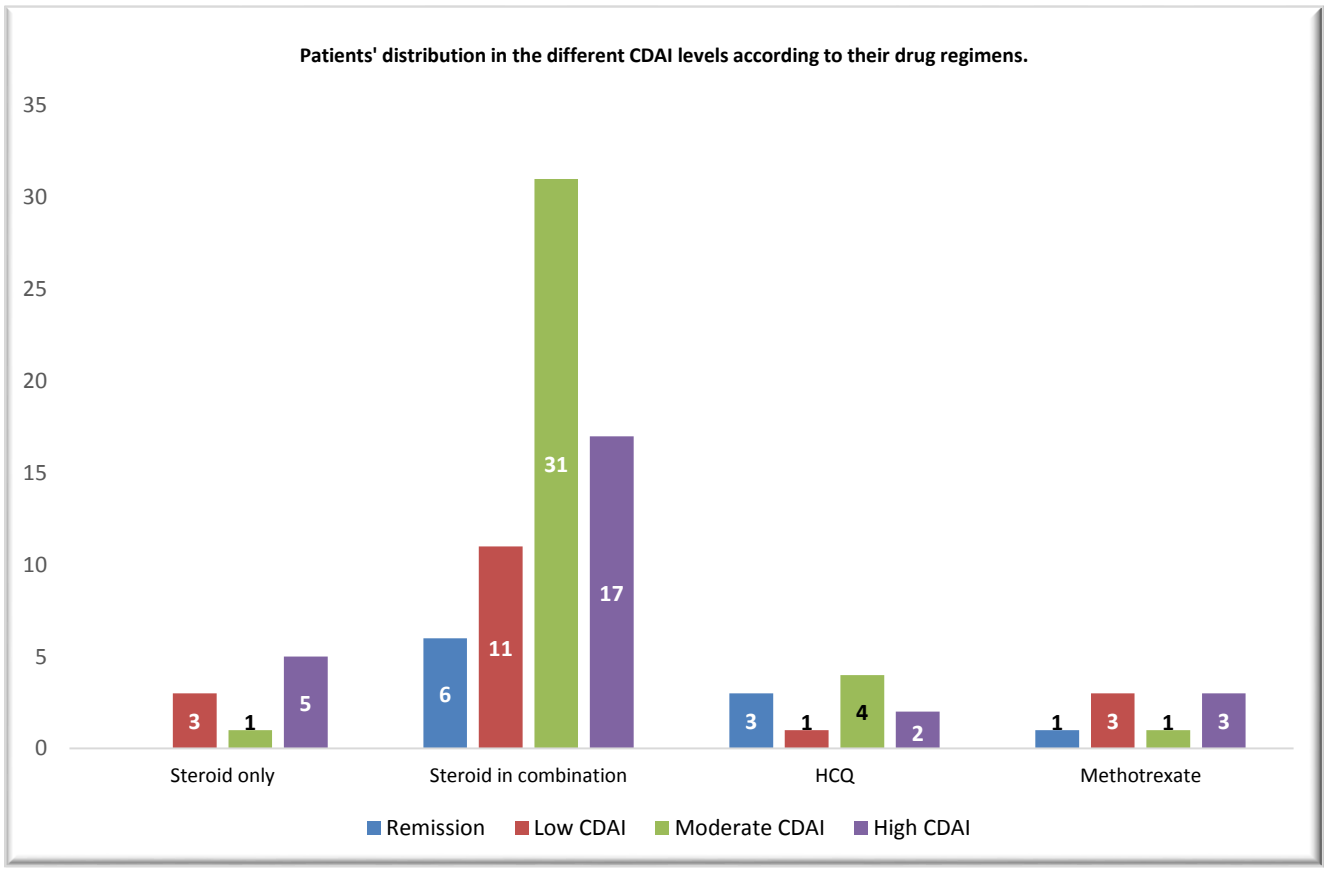

Figure 2: CDAI score for major group classes. Numbers of patients only exhibited.

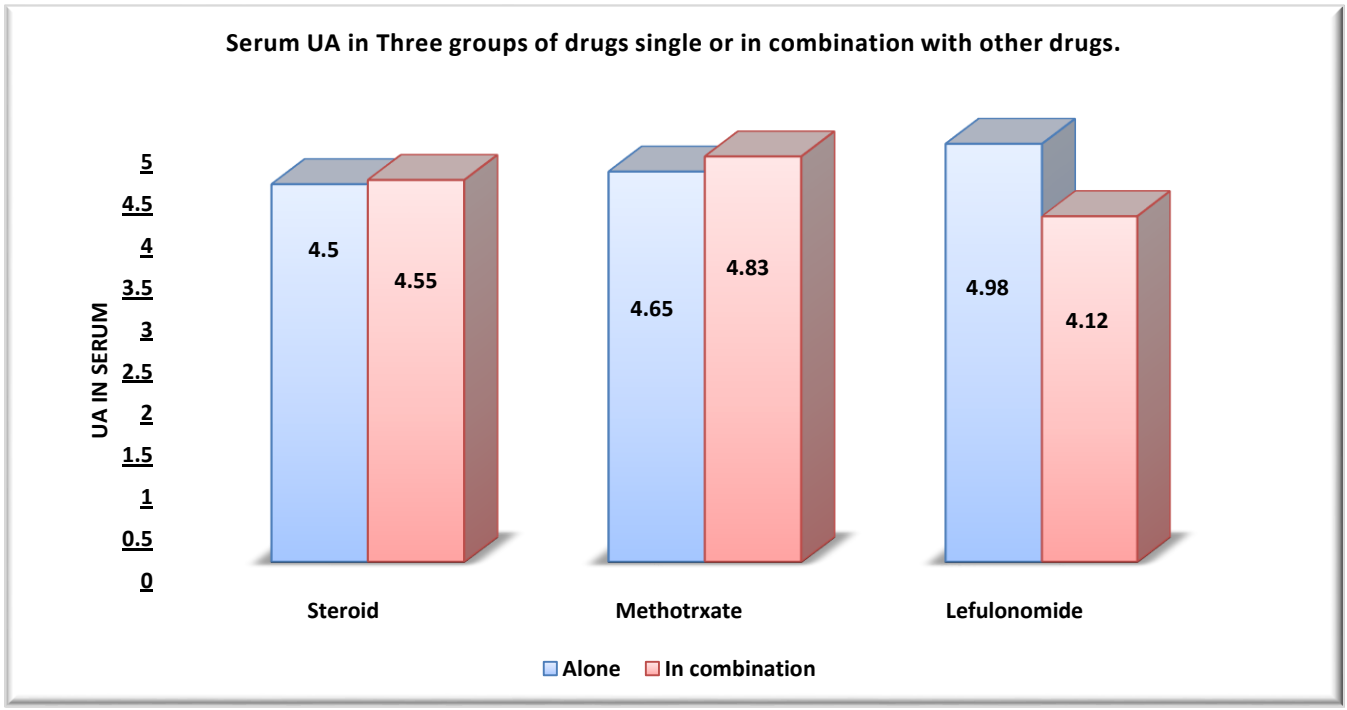

Figure 3: comparing serum UA levels in three main drugs; Steroids, Methotrexaye, and lefulonomide, either alone or combined with other drugs. Diffrence was insignificant.

Discussion.

CDAI is a composite index for quantifying disease activity in RA. It has been developed from the disease activity index DAS, and it is preferable in the account that it does not require any laboratory assessment (4). CDAI utilizes four clinical parameters namely, swollen and tender joints- out of 28 joint, global assessment of the patient and assessor on a visual analogue scale (5).The CDAI is the only composite index that does not incorporate an acute phase response and can therefore be used to conduct a disease activity evaluation essentially anytime and anywhere (6). It is one of five measures that has been recommended by the American college of rheumatology, the others are: 28-joint Disease Activity Score (DAS28-ESR/CRP), Simplified Disease Activity Index (SDAI), Routine Assessment of Patient Index Data 3 (RAPID3), and Patient Activity Scale-II (PAS-II) (7). In CDAI, the lower the value, the better is the prognosis. Two disadvantages of CDAI is the non-involvement of the ankle and feet in assessment, and the absence of investigation. The score interpretation adopted in our research was: ≤2.8 as a remission; >2.8 and ≤10 as a low Disease Activity; >10 and ≤22 as a moderate Disease Activity; and >22 as a high Disease Activity. In this current study, the use of steroid in combination, particularly with HCQ, gave higher remission rate and lower percent of patients were in high index than those using steroid only. In the eight patients taking Methotrexate, one (12.5%) was on remission and three (37.5%) were with a high CDAI, and the remaining three groups were inferior when compared to HCQ group. As mentioned by Choe and Kim in 2015, Lefulonomide has a potential to lower serum UA. This may attribute to the reduction of inflammatory status and hence improvement of CDAI: an explanation that Choe and Kim had rejected (4). In our current study, Lefulonomide caused lowering in serum UA in the patients only when used in combination with Steroid or HCQ, and the result was statistically insignificant. See figure 3.

In Kirwan et al review of 2005, all studies except one showed a numerical treatment effect in favor of steroids. Their beneficial effects were generally achieved when used in conjunction with other DMARD treatment. Steroids given in addition to standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis is convincing. There remains concern about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk, and this issue requires further research (8), and, as remarked by Gotzsche and Johansen, the steroid Prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means (9). As seen in our current study, Steroids in combination gave a better results, putting more patients in remission and at the same time, less percent was in the high disease index (see the results text and figure 2).

In 2014, Smolen et al classified DMARDs into Biological and Synthetic, the former is sub classified into original biological or bio-similar, while the synthetic is further r divided into conventional or targeted synthetic (10). In our current study, there were only conventional synthetic DMARDs as they are the common prescriptions in Sudan.

Methotrexate is a well-known DMARD and very common to be used in a combination for the management of RA. According to 2015 NICE (11) and the 2015 American College of Rheumatology guidelines (12), Methotrexate is the most important and useful DMARD and is usually the first treatment. In this study, one patient using methotrexate was on remission and three had a high CDAI score. Paradoxically, three of the four patients on methotrexate alone had a mild disease CDAI, and three of the four patients using Methotrxate in combination with HCQ had a high CDAI index. This opposes the results obtained by Schapink et al in 2019, where Methotrxate–HCQ combination proved to be more effective after 6 months than MTX monotherapy in early RA patients, however, there was no significant difference between the two groups after one year (13). The previous study have the upper hand when compared with our own study, as there were more than thirty folds the sample size for Methotrxate and HCQ (325 patients), and the samples were re-taken twice.

In our study, 67% of the patients using Lefulonomide alone were on remission, and 33%had a high CDAI. While in the patients using Lefulonomide in combination with steroids, one patient (6%) was on remission while eight (50%) had a high CDAI. There were five (31%) having a moderate CDAI, and two (13%) with a low CDAI. The result, however, lacks the presence of an adequate sample size, as the former group contained only 3 patients and the later contained 19 patients.

Although the differences in mean serum UA levels between the groups using different drug regimens was insignificant, some attention should be paid to the Lefulonomide group that recorded the lowest mean UA, as the result agrees with previous studies(4, 14)

Study limitations:

1. The small sample size with inadequate distribution ofmedication, as most of the patients-two thirds-are using steroids.
2. The study design, which is a cross sectional while in this case, a prospective randomized controlled trial is more suitable.
3. In addition, the patients' serologies were not determined.

Conclusion.

This study was executed to measure two variables in association with the common drug described for RA in Sudan: the uric acid levels, and the clinical disease activity index. The drug regimens were classified into five major groups: Steroids, Hydroxychloroquine, Lefulonomide, and Methotrexate. The overall result was Lefulono-dmide gave the highest rate of remission and the lowest serum UA mean, while HCQ gave the least

percent of severe CDAI. There must be further studies for drug effects in these variables.

References.

1- Chauhan K, Jandu JS, Goyal A, et al. Rheumatoid Arthritis. [Updated 2022 Jun 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441999/

2- Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2018;27(6):501-507. doi: 10.1159/000493390. Epub 2018 Sep 2. PMID: 30173215; PMCID: PMC6422329.

3- Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder R, Woolf A, March L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul;73(7):1316-22. doi:10.1136/ annrheumdis - 2013-204627. Epub 2014 Feb 18. PMID: 24550173.

4- Choe JY, Kim SK. Association between serum uric acid and inflammation in rheumatoid arthritis: perspective on lowering serum uric acid of leflunomide. Clin Chim Acta. 2015 Jan 1;438:29-34. doi: 10.1016/j.cca.2014.07.039. Epub 2014 Aug 7. PMID: 25108207.

5- Arya V, Malaviya AN, Raja RR. CDAI (clinical disease activity index) in rheumatoid arthritis: cut-off values for classification into different grades of disease activity. In J Rheum. 2007;2(3): 91-94. https://doi.org/10.1016/S0973-3698(10)60091-X

6- Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep-Oct;23(5 Suppl 39):S100-8. PMID: 16273793.

7- England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR, O'Dell JR, Ranganath VK, Limanni A, Suter LG, Michaud K. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). 2019 Dec;71(12):1540-1555. doi: 10.1002/acr.24042. Epub 2019 Nov 11. PMID: 31709779; PMCID: PMC6884664.

8- Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane DatabaseSystRev.2007Jan24;2007(1):CD 006356 doi:10.1002/14651858.CD006356.PMID:17253590; PMCID: PMC6465045.

9- Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Cochrane Database Syst Rev. 2002;(2):CD000189.doi: 0.1002/14651858.CD000189. Update in: Cochrane Database Syst Rev.2003;(1): CD000189. PMID: 12076385.

10- Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014 Jan;73(1):3–5. doi:10.1136/annrheumdis-2013-204317

11- "Rheumatoid arthritis in adults: management: recommendations: Guidance and guidelines". NICE. December 2015. Archived from the original on 2017-04-16.

https://web.archive.org/web/20170416130024/https://www.nice.org.uk/guidance/CG79/chapter/Recommendations#

12- Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6. PMID: 26545940.

13- Schapink L, van den Ende CHM, Gevers LAHA, van Ede AE, den Broeder AA. The effects of methotrexate and hydroxychloroquine combination therapy vs methotrexate monotherapy in early rheumatoid arthritis patients. Rheumatology. 2019: 58(1): 131–134. https://doi.org/10.1093/rheumatology/key275

14- Costa NT, Scavuzzi BM, Iriyoda TMV, Lozovoy MAB, Alfieri DF, de Medeiros FA, de Sá MC, Micheletti PL, Sekiguchi BA, Reiche EMV, Maes M, Simão ANC, Dichi I. Metabolic syndrome and the decreased levels of uric acid by leflunomide favor redox imbalance in patients with rheumatoid arthritis. Clin Exp Med. 2018 Aug;18(3):363-372. doi: 10.1007/s10238-018-0500-y. Epub 2018 Apr 11. PMID: 29644482.