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# Disease Modifying Anti Rheumatic Drugs in Sudanese Patients with Rheumatoid Arthritis

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**Abstract** **Objectives:** To know about DMARDs (Disease modifying anti rheumatic drugs) used by Sudanese rheumatoid arthritis patients, the type mostly used, single or combined and to assess functional disability by health assessment questionnaire (HAQ) and disease activity by clinical disease activity index (CDAI) with each type used and the time of initiation of DMARDs therapy from the diagnosis, also to see the effect of combined therapy on functional disability and disease activity. **Materials and Methods:** This was descriptive cross sectional study hospital based of 100 patients diagnosed as RA by the American College of Rheumatology (ACR-EURAL 2010) criteria attending different rheumatology referred clinics from Nov 2014to Jan 2015 patients were interviewed and asked about their DMARDs which type is used and when it started from the time of diagnosis then HAQ is filled and CDAI is calculated. **Results:** We had analyzed 100 patients the type of their DMARD, HAQ, CDAI the time of initiation of DMARDs with the diagnosis effect on HAQ and CDAI, also the effect of combined therapy on HAQ and CDAI. We found that the age between 36-45 were mostly affected and that 95% was female. 71% were using Hydroxychloroqine (HCQ), 49% Methotrexate (MTX), 6% Leflounimide (LEFLU), 2% Sulphasalzine and 3% Azathioprine (AZA). Most patients showed minimal HAQ (69.0%) score, 64% of the study population start DMARD at the time of diagnosis. About 36% used combined MTX and HCQ. Low CDAI was the most common in patients taking MTX and HCQ, also the most common score of HAQ in them was minimal score. There is no significant difference (P value 0.23) between early initiation of DMARDs and disease activity, also the difference was not significant between the time of initiation of DMARDs and HAQ score (P 0.036). There is significant difference between the use of combined DMARDs and CDAI and HAQ score (P 0.001, P 0.004) respectively. **Conclusion:** The most commonly used DMARDs are HCQ and MTX, Combination therapy is not widely used in the study patient, Most of the study patients show minimal functional disability assessed by HAQ. MTX and HCQ affect disease activity and functional disability almost in the same manner, patients in the study using MTX and HCQ show minimal score using HAQ, small percentage show remission and no remission with other type of DMARDs. Early initiation of DMARDs doesn't affect functional disability and disease activity. While combination therapy of DMARDs affect both disease activity assessed by CDAI and functional disability assed by HAQ score.

**Keywords** DMARDs, CDAI

## 1. Introduction and Literature Review

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that primarily affects joints' it may result in deformed and painful joints, which can lead to loss of function, it may also have signs and symptoms in organs other than joint [1]. Rheumatoid arthritis (RA) affects approximately 1% of the UK adult population, its incidence is two to three times greater in women, and this disparity is most pronounced in patients younger than 50 years, although rheumatoid arthritis may present at any age, patients most commonly affected in the third to sixth decades [1].

### 1.1. Clinical Features

The arthritis is symmetrical and may be remitting, the disease onset isusually insidious, with the predominant symptoms being pain, stiffness, and swelling of many joints, the disease usually progresses from the periphery to more proximal joints, and it is usually insidious [2]. Typically, the metacarpophalangeal and proximal interphalangeal joints of the fingers, interphalangeal joints of the thumbs, the wrists, and metatarsophalangeal joints of the toes are sites of arthritis early in the disease. Other joints of the upper and

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lower limbs, such as the elbows, shoulders, ankles, and knees are also commonly affected [3,4].

Extra-articular involvement consists of the musculoskeletal system other than joints (e.g. bone and muscle) and of organs not considered part of the musculoskeletal system (e.g. skin, eye, lung, heart, kidney, blood vessels, salivary glands, central and peripheral nervous systems, and bone marrow) occurs in about 40 percent of patients with RA over a lifetime of disease [5,6] Anemia, fatigue, subcutaneous ("rheumatoid") nodules, pleuropericarditis, neuropathy, episcleritis, scleritis, splenomegaly, Sjögren's syndrome, vasculitis, and renal disease, may occur during the course of the disease [6].

### 1.2. The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis

Classification criteria for RA (score-based algorithm: add score of categories A to D (a score of ≥6/10 is needed for classification of a patient as having definite RA)

**A. Joint involvement**

1 large joint.....0

2-10 large joints ……...1

1-3 small joints (with or without involvement of large joints) …. ……2

4-10 small joints (with or without involvement of large joints)…… 3

>10 joints (at least 1 small joint)

……..……5

**B. Serology:** at least 1 test result is needed for classification

Negative RF *and* negative ACPA ……0

Low-positive RF *or* low-positive ACPA …….....2

High-positive RF *or* high-positive APA ……...3

**C. Acute-phase reactants** (at least 1 test result is needed for classification)

Normal CRP *and* normal ESR ……0

Abnormal CRP *or* abnormal ESR ……..1

**D. Duration of symptoms**

<6 weeks ……..0

≥6 weeks ……..1

Explanatory points in the ACR-EULAR classification criteria:-

- Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.
- Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis.
- Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment.
- "Large joints" refers to shoulders, elbows, hips, knees, and ankles.
- "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists.
- When > 10 joints involved, at least 1 of the involved joints must be a small joint.
- Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay.
- Low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay.
- High-positive refers to IU values that are >3 times the ULN for the laboratory and assay.
- Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
- Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

### 1.3. Treatment of Rheumatoid Arthritis (RA)

The treatment of rheumatoid arthritis (RA) is directed toward the control of synovitis and the prevention of joint injury. The choice of therapies depends upon several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions [7].

**a) Non pharmacologic therapies:** A number of non pharmacologic measures and other medical interventions are important in the comprehensive management of RA in all stages of disease, in addition to anti inflammatory and anti rheumatic drug therapies such as:

- Patient education
- Psychosocial interventions
- Rest, exercise, and physical and occupational therapy
- Nutritional and dietary counseling
- Immunizations
- Surgery such as total joint replacement, tendon repair and joint fusion.

**b) Pharmacologic therapy:** Choices between treatment options are based upon multiple factors, including level of disease activity, stage of therapy, regulatory restrictions patient preferences.

Many drugs used to treat rheumatoid arthritis:

- NSAID: Non steroidal anti-inflammatory drugs (NSAIDs) can relieve pain and reduce inflammation, include ibuprofen and naproxen sodium.
- Steroids: such as prednisone, reduce inflammation and pain and slow joint damage.
- Disease-modifying anti rheumatic drugs (DMARDs).

**Disease modifying anti rheumatic drugs (DMARD):**

a) **Conventional DMARDs (non biological):** Disease-modifying anti rheumatic drugs (DMARDs) are a group of medications commonly used in patients

with rheumatoid arthritis. Some of these drugs are also used in treating other conditions such as ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus [7]. It has been for many decades and stills the mainstay of RA treatment, ameliorate clinical symptoms, reduce joint damage and allow a subset of patients to achieve remission [7]. These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from permanent damage. Commonly used Methotrexate, Leflunomide, Hydroxychloroquine and Sulfasalazine. Side effects vary but may include liver damage, bone marrow suppression and severe lung infections.

b) **Biologic agents:** The introduction of biologic agents; particularly biologic agent and conventional DMARD combinations, has resulted in further improvements in clinical outcome and greater effect on disease activity, functional capacity and structural damage [8]. This newer class of DMARDs includes Abatacept, Adalimumab, Anakinra, Certolizumab, Etanercept, Golimumab, Infliximab, Rituximab and Tocilizumab. These drugs can target parts of the immune system that trigger inflammation that causes joint and tissue damage, these types of drugs also increase the risk of infections [8].

**`How do disease-modifying anti rheumatic drugs (DMARDs) work?**

DMARDs work to suppress the body's overactive immune and/or inflammatory systems. They take effect over weeks or months and are not designed to provide immediate relief of symptoms [9]. Improved clinical outcome. Van Der Heide and colleagues completed a study in which 238 patients who had RA for less than one year were randomized to receive either a DMARD or a non steroidal anti-inflammatory drug. The primary study endpoints were functional disability, pain, joint score, and erythrocyte sedimentation rate (ESR) at 6 and 12 months, as well as progression [9]. At the end of 12 months, patients who had received DMARD experienced clinically important improvement in disability, pain, joint score, and ESR, compared with patients in whom DMARD were postponed. DMARD treatment also produced improvement at 6 months. Radiographic abnormalities progressed in both groups, but were worse in the non-DMARD group. The investigators concluded that immediate introduction of DMARD may produce the most effective results in patients with early RA [9].

i. **Methotrexate**: Was originally used as a chemotherapy treatment for cancer, it is an anti proliferative and immunosuppressive; It is usually taken once per week as a pill, liquid, or injection. Methotrexate may be combined with other DMARDs or with a biologic agent if Methotrexate alone does not adequately control a patient's disease [9]. Common side effects include: upset stomach and a sore mouth, decrease bone marrow's production of blood cells and liver or lung damage. Monitoring reduces the risk of long-term damage by chest x-ray and regular blood testing. People using Methotrexate are strongly discouraged from drinking alcoholic beverages because of the increased risk of liver damage with this combination. While taking Methotrexate, most patients take Folic Acid 1 mg daily or Folinic Acid 5 mg weekly to reduce the risk of certain side effects [9].

ii. **Hydroxychloroquine:** Developed as a treatment for malaria, was later found to improve symptoms of arthritis. It acts by changing intracellular PH. It can be used early in the course of rheumatoid arthritis and is often used in combination with other DMARDs or steroid. It can be taken in pill form once or twice per day [9]. Taking a high dose of Hydroxychloroquine for prolonged periods of time may increase the risk of damage to the retina of the eye. It is common to have an eye check-up done once each year [9].

iii. **Sulfasalazine:** is used in the treatment of rheumatoid arthritis and of arthritis associated with Ankylosing Spondylitis and inflammatory bowel disease.It is not clear how Sulfasalazine works [9]. People who are allergic to sulfa drugs may have a cross reaction to Sulfasalazine and should, therefore, not take it. It is taken as a pill two to four times per day, and it is usually started at a low dose and is increased slowly to minimize side effects, which include changes in blood counts, nausea or vomiting, sensitivity to sunlight, skin rash, and headaches, Orange tinge of urine and tears. Periodic blood tests are recommended to monitor the blood count on a regular basis [9].

iv. **Leflunomide**: It is taken by mouth once daily. Side effects include rash, temporary hair loss, liver damage, nausea, diarrhea, weight loss, and abdominal pain. Regular testing to monitor for liver damage is required [9].

v. **Azathioprine**: is generally reserved for patients who have not responded to other treatments. The most common side effects of AZA include nausea, vomiting, decreased appetite, liver function abnormalities, low white blood cell counts, and infection. It is usually taken by mouth once to four times daily. Blood testing is recommended during treatment with AZA [9].

vi. **Cyclosporine:** It works in patients with rheumatoid arthritis to inhibit T lymphocytes, a cell that contributes to the inflammation.Its associated with kidney disease and high blood pressure, It is usually taken by mouth in pill or liquid form twice per day; an injectable form is also available. Side effects include high blood pressure, swelling, kidney damage, increased hair growth, nausea, diarrhea, and heartburn and needs blood pressure and kidney function monitoring on a regular basis [9].

**When are disease-modifying anti rheumatic drugs (DMARDs) usually prescribed?**

DMARDs are prescribed as soon as possible after RA has been diagnosed. Studies indicate that initiating treatment

with disease modifying anti rheumatic drugs (DMARD) as soon as possible after diagnosis produces significant clinical and functional benefit and appears to retard the rate of radiographic progression of erosions. Delaying treatment by as little as 8 or 9 months sets the stage for damage that cannot be reversed [10]. In particular, early treatment with disease modifying anti rheumatic drugs (DMARD) can reverse morbidity, as measured by disability and radiographic progression of joint damage. Determining when patients with RA are most responsive to treatment was the subject of a 2 year, double blind, placebo controlled trial conducted by Borg and colleagues [11]. All 137 study participants had RA for less than 2 years. "Early" treatment (as soon as possible after diagnosis) with Auranofin was compared with DMARD treatment that was started after clinical deterioration was evident (about an 8 month delay). By the end of the second year, early treatment had produced significantly greater improvement in physical function than delayed treatment [11].

Also mentioned in clinical review done by BMJ in treatment of rheumatoid arthritis where mentioned early With the establishment of clinics for dealing with early arthritis it was clear that earlier intervention produced a better outcome. A case-control parallel-group study, 20 very early RA (VERA) patients with median disease duration of 3 months were age and gender matched to a group of 20 late early RA (LERA) patients with median disease duration of 12 months until first DMARD initiation. Follow-up time was 36 months. Primary outcome measures were the disease activity score (DAS28) and radiological joint destruction using the Larsen method. Concluded that there is a window of opportunity for highly successful treatment of RA in the first year, and especially within the first 3 months of therapy. Thus, early diagnosis and therapy may be the crucial step in achieving optimal control of disease progression and prognosis in RA [12].

**When to refer to specialist?**

Early referral is important as seen in study done by Professor P Emery, Department of Rheumatology and Rehabilitation Accepted 29 August 2001 Annual of rheumatic disease the Eural journal reported that to develop a referral recommendation that may serve as a clinical guide for primary care doctors, enabling them to identify patients with suspected RA during the early inflammatory stages [13]. Clinical evidence strongly supports the observations that structural damage occurs early in active RA and that early DMARD treatment improves the long term outcome of the disease. The observations indicate that rapid referral to a rheumatologist is advised when RA is suspected. This may be supported by the presence of any of the following: ≥3swollen joints, metatarsophalangeal/metacarpophalangeal involvement, and morning stiffness of ≥30 minutes. Early referral to a rheumatologist for definitive diagnosis and early DMARD treatment should improve the long term outcome of RA [14].

**Choice of medicine:** The choice of medicine will depend on many issues. It can take several weeks or months for DMARDs to ease the pain and inflammation caused by RA. In general, Methotrexate and Sulfasalazine are better tolerated and have less serious side-effects [15]. Methotrexate is the DMARD most often chosen for initial treatment Current Opinion in Rheumatology, May 1999 Disease-modifying anti rheumatic drugs reported that. Methotrexate remains the most popular disease-modifying anti rheumatic drug and is used in the most popular combination treatments, although the dose needs to be reduced in the elderly and those with renal dysfunction. The combination of Sulfasalazine, Methotrexate with reducing high-dose Prednisolone, is demonstrated to be cost-effective in patients with rheumatoid arthritis, but although several other combinations have been reported effective in patients with rheumatoid arthritis, most trials do not have the power to provide a definitive answer as to the best combination available, if one exists [15].

**COMBINATION OF DMARD:** Combination of DMARD is better than monotherapy, COBRA Combinatietherapie Bij Reumatoide Artritis (COBRA) trial were published in 1997 In the original COBRA trial, 155 patients with early RA (median duration 4 months) were randomized to receive either combination therapy with Sulfasalazine (2 gm/day), Methotrexate (7.5 mg/week), and Prednisolone or Sulfasalazine alone. Prednisolone was given in a dosage of 60 mg/day for the first week and then rapidly tapered to 7.5 mg/day. Prednisolone was stopped after week 28, and Methotrexate was stopped after week 40. After that point, all patients received similar treatment. They report that patients in the original combination-therapy group had less radiologic progression at 4 years compared with the original monotherapy group, and, more important, their disease continues to progress at a slower rate [16].

The important findings of the COBRA trial are the following: inflammation can be suppressed quickly in early RA, benefiting patients for at least the duration of the suppression; 2) combination therapy is not necessarily more toxic than monotherapy (more withdrawals occurred in the Sulfasalazine-alone group); and 3) when induction therapy is stopped, patients who have received it begin to clinically resemble those who have not [16]. The vast majority of trials that have compared combination DMARD therapy with DMARD monotherapy in early RA have shown superior outcomes for the groups treated with combinations in addition to the COBRA trial, these include the Finnish Rheumatoid Arthritis Combination Therapy Trial, in which the combination of Methotrexate-Sulfasalazine-Hydroxychl oroquine and Prednisolone was superior to Sulfasalazine with or without Prednisolone, and the trial by Calguneri et al, in which triple therapy with Methotrexate-Sulfasalazine-Hy droxychloroquine was superior to 2-drug combinations, and 2-drug combinations were superior to monotherapy. Furthermore, the results of the study by Kirwan and colleagues, in which the addition of Prednisolone to conventional therapy slowed radiologic progression compared with conventional therapy alone, also support use of combination DMARD therapy. Therefore, although all

available data support use of combination DMARD therapy in early RA, most clinicians favor the approach of rapidly stepping up DMARD therapy in those patients who have suboptimal responses to DMARD monotherapy [16].

### 1.4. Functional Disability Assessment in Rheumatoid Arthritis

Is an important determinant of the natural history of RA and is a useful tool for assessing the effectiveness of therapeutic interventions, many instruments for patient evaluation have been developed, the two physical function assessment tools used most frequently are [20]:

- The Health Assessment Questionnaire (HAQ).
- The Medical Outcomes Study Short Form-36 (SF-36).

**The Health Assessment Questionnaire (HAQ)**

Originally was developed in 1978 by James F. Fries, MD and colleagues at Stanford University. It was one of the first self-report functional status (disability) measures and has become the dominant instrument in many disease areas, including arthritis. It is widely used throughout the world and has become a mandated outcome measure for clinical trials in rheumatoid arthritis and some other diseases [20].

The HAQ has been administered primarily in one of two versions, the 2-page or short HAQ-DI (Disability Index) or the Full HAQ. The Full HAQ is a multi-dimensional instrument. It contains five sections which address generic health dimensions, or the "5 Ds": disability; discomfort; drug toxicity; health care utilization and cost ("dollars"); and death. It also includes supplemental items on demographics, lifestyle, and health behaviors [20].

The 2-page HAQ-DI has received the widest attention, the most frequent use, and is the most cited version. It is commonly called "the HAQ", and consists of:-

- The HAQ DI.
- The HAQ Pain Visual Analog Scale (VAS).
- The Patient Global Health VAS.

The HAQ DI was used in a study where a total of 6,610 patients were enrolled in the ReAct trial: 81% were female, 73% were RF positive, 74% were taking at least 1 concomitant DMARD, and 71% were receiving Glucocorticoids. Additional baseline characteristics included a mean age of 54 years, mean disease duration of 11 years, mean DAS28 score of 6.0, and mean HAQ DI score of 1.64 [20].

**Statistical analysis of the health assessment questionnaire (HAQ)**

The Health assessment questionnaire disability index (HAQ-DI) is a questionnaire for the assessment of Rheumatoid Arthritis. The questionnaire is a patient reported outcome (PRO) which is usually self-administered by the patient.

The following categories are assessed by the HAQ-DI:

1. Dressing and grooming
2. Arising
3. Eating
4. Walking
5. Hygiene
6. Reach
7. Grip
8. Common daily activities

The patients report the amount of difficulty they have in performing some of these activities. Each question asks on a scale ranging from 0 to 3 if the categories can be performed without any difficulty (scale 0) up to cannot be done at all (scale 3). For each of the eight disability categories there is an AIDS OR DEVICES companion variable(s) that is used to record the type of assistance, if any, a patient uses for his/her usual activities. When there are NO aids or devices or help indicated for a category, the category's score is not modified. When aids or devices or help are indicated by the patient, the score for the category item is raised from a 0 or a 1 to a 2, but if the patient's highest score for that sub-category is a 3, it stays a 3, So, the analysis requires linking results from aids or devices variables back to the disability category [17].

Improperly Marked Items: When a patient makes a mark between two response options, then the score is the closest one. When it is directly between two response options, use the higher number. Items Left Blank: When all sub-category items in a category are left blank, or when more than one response is given, then follow up with the patient is required [18].

The he HAQ Pain Scale assesses arthritis-related pain and its severity over the PAST WEEK on a double-anchored VAS, the VAS line is standardized to 15 centimeters in length, which is convenient for the page and the patient. The scale is labeled from zero (no pain) at the left anchor point and 100 (severe pain) at the right anchor point [18,19].

Patients are instructed to place a vertical mark on the line to indicate the severity of their pain. Using a metric ruler; from zero to the patient's mark, measure the distance in centimeters and multiply by 0.2. This converts centimeters into the appropriate metric and yields a score from 0 to 3.

The Global VAS is also a 15-centimeter, double-anchored horizontal scale that starts at 0 (very well) and goes to 100 (very poor). Handling responses and scoring are the same as the Pain Scale [18,19].

**INTERPRETATION OF THE HAQ:**

0-1 remission
1-2 mininal
2-3 moderate

### 1.5. Disease Activity in Rheumatoid Arthritis

Internationally developed recommendations suggest frequent measurement of disease activity to facilitate achievement of remission in the fastest possible manner [21].

Disease activity in patient with RA can be measured using different scores:

- ACR response criteria.
- The Disease Activity Score (DAS), its derivative (the

DAS28).

- The Simplified Disease Activity Index (SDAI).
- The Clinical Disease Activity Index (CDAI).

Baseline disease activity by these composite scores and especially disease activity after three months of therapy with DMARDs is highly predictive of disease activity at later points in the time (one year) allowing adopting treatment strategies [21].

1.5.1. Disease Activity Score (DAS)

Several features make the DAS challenging to use in clinical trial and practice setting, it employs the Ritchie Articular Index, a measure with major short comings in terms of feasibility and reliability, to evaluate joint tenderness [22]. The DAS employs an extensive 44 joint count to record the number of swollen joints. The formula for calculating the score is quite complex.

DAS28 is considerably more practical. The DAS28 eliminated the grading of joints and reduced the number of joints evaluated to 28; it has largely replaced the traditional DAS in clinical trials and in practice. The DAS28 can be calculated using the complex formula but it can easily be calculated using a preprogrammed calculator or other computing devices like our Web calculator or programmed MS Excel.

One characteristic of the DAS28 is the greater relative weight it gives to measures of the acute phase response. it also gives half as much weight to a swollen joint as it does to a tender joint, although both have a similar level of severity of inflammation.

1.5.2. ACR Response Criteria

An early attempt to define minimal response requirements [23]. These criteria formed the basis for the ACR response criteria which (in their initial iteration) outlined the variables of a 20 percent improvement. The ACR20 response is defined as improvement of at least 20 percent in the number of both swollen and tender joints, as well as at least 20 percent improvement in three or more of the five remaining core set variable ACR50 and ACR70 developed [24].

1.5.3. Simplified Disease Activity Index (SDAI)

The SDAI is defined as the simple sum of the, tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0 to 10 scale), physician global assessment (0 to 10 scale) and C-reactive protein level (mg/dL).

1.5.4. Clinical Disease Activity Index (CDAI)

The CDAI is a simplified assessment scale that is sensitive to changes in disease activity, is easier to calculate and use in clinical practice [25]. it does not require laboratory measurement of acute phase reactants, allowing for more immediate therapeutic decisions [25,26] CDAI may be a better target than DAS-28.

1.5.5. The Advantages of the CDAI are that

- It facilitates immediate treatment decisions based entirely on clinical criteria and includes assessment of the joints, the principle “target organ" in RA.
- It circumvents the potential problem of lab to lab variation in the measurement of acute phase reactants.
- A calculator for the CDAI is available.

**CDAI = SJC (28) + TJC (28) + PGA + EGA**

- SJC (28): Swollen 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees)
- TJC (28): Tender 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees)
- PGA: Patient Global disease Activity (patient’s self assessment of overall RA disease activity on a scale 1-10 where 10 is maximal activity)
- EGA: Evaluator’s Global disease Activity (evaluator’s assessment of overall RA disease activity on a scale 1-10 where 10 is maximal activity)

**Interpretation**

- Remission CDAI ≤ 2.8
- Low Disease Activity CDAI > 2.8 and ≤ 10
- Moderate Disease Activity CDAI 11 and ≤ 22
- High Disease Activity CDAI > 22

**Deficiencies**

- Does not include the ankles / feet
- Does not include inflammatory markers (although this is what makes it a quick and useful clinical tool)

Internationally developed recommendations suggest frequent measurement of disease activity to facilitate achievement of remission in the fastest possible manner [12,27]. These recommendations are based on data suggesting that early and aggressive therapy is associated with improved clinical outcomes. The Tight Control for Rheumatoid Arthritis (TICORA) study demonstrated that tight control and clinical measurement of disease were associated with disease remission and a decreased risk of radiographic progression [27]. In this single-blind study, patients were randomly assigned to routine outpatient care (control) or intensive outpatient care with conventional DMARDs and were followed up for 18 months. The routine care group was seen every 3 months; no formal composite disease activity measure was used to guide clinical decisions. Intensive care consisted of monthly outpatient assessments—objective assessment of disease activity, IA CS injections and the targeting of persistent disease activity using a protocol to escalate DMARD therapy. At 18 months, patients in the intensive care group had achieved significantly higher ACR 20/50/70 responses (91%/84%/71%) than had the routine care group (64%/40%/18%; $P < 0.0001$ for all comparisons) [27]. The percentages of patients reaching good European League against Rheumatism (EULAR) response (i.e. DAS <2.4, 82 Vs 44%; $P < 0.0001$) and remission (DAS < 1.6, 65 Vs 16%; $P < 0.0001$) also were significantly higher in the intensive

care group. Further, radiographic progression, as assessed by total Sharp scores and erosion scores, was significantly reduced in the intensive care group compared with the routine care group [27]. An initial treatment algorithm that incorporates the goal of achieving rapid disease remission. This proposed algorithm was derived from recommendations based on evidence from five literature reviews performed for synthetic DMARDs, biologic DMARDs and Glucocorticoid treatment strategies. The literature reviews were discussed and summarized as an expert opinion in the course of a Delphi-like process. The algorithm recommends early initial and intensive therapy with high-dose MTX therapy, which may include moderate doses of Glucocorticoids [6]. The goal is to achieve low disease activity (determined by a composite measure of disease activity that includes joint counts such as DAS-28, SDAI and CDAI; within 3–6 months [27].

For patients who do not exhibit any improvement by 3 months, treatment should be adjusted immediately; for those who exhibit improvement within this time frame but do not achieve DAS, SDAI or CDAI low disease activity, an additional 3 months of observation is warranted [27].

If low disease activity or remission is not achieved by 6 months, another conventional DMARD or biologic agent should be added to the treatment regimen or patients should be switched to another DMARD plus a Glucocorticoid [27].

Several published studies favor the addition of a biologic agent in MTX inadequate responders over the use of SSZ in addition to MTX. Once low disease activity is achieved, the treatment goal over the ensuing 3–6 months becomes disease remission if the disease is in the early stages and reversible damage is not significant [28].

## 2. Methodology

**i. Study design:** Descriptive prospective cross sectional study hospital based.

**ii. Study area:** The patients from referred clinics of rheumatology at Khartoum city, the capital of Sudan in Omdurman Military hospital, Alribat hospital and Omdurman teaching hospital.

**iii. Study population:** Patients diagnosed as having rheumatoid arthritis using ACR –EURAL criteria 2010.

a) **Inclusion criteria:** Patient diagnosed clinically with rheumatoid arthritis fulfilling the Criteria of the American College of Rheumatology classification 2010and taking DMARD
b) **Exclusion criteria:** Patients who were diagnosed as RA and not taking DMARD and Patients who were unwilling to participate in the study.

**iv. Sample size:** 100 patients.

**v. Study period:** November 2014 to January 2015.

**vi. Methods and tools:** Patients interviewed and asked about which DMARD have been used, the duration of diagnosing RA and the time of initiation of DMARD in relation to the diagnosis. The disease activity will be assessed by CDAI using the formula and online calculator

**CDAI = SJC (28) + TJC (28) + PGA + EGA**

Functional disability will be assessed by HAQ in appendix

**vii. Data collection**: Data collected by the following:

a. Patient interviewing to take history
b. Patient assessment that fills the CDAI.
c. Patient assessment that fills the HAQ.

**viii. Data analysis and management:**

- The data presented as number and percentage. The results, whenever possible, will be analyzed by differences between percentages and simple correlation taking $P<0.05$ as the limit of significance, using Microsoft excel 2013 and SPSS v19 programs.
- The health assessment questionnaire was analyzed by marking the health assessment questionnaire disability index by give each category from the eight marks the mark given by the patient the collection is divided by eight, for pain and global visual analog scale the line written by the patient is calculated in cm then multiplied by 0.2 then change from cm by using appendix.

**ix. Ethical considerations:**

Approval was taken from local ethical committee and administration of the study area, all participants had an informed verbal consent, and the purpose of the study had been explained. The information gathered was kept confidential.

## 3. Results

100 patients were analyzed according to the type of their DMARD, HAQ, CDAI the time of initiation of DMARDs with the diagnosis effect on HAQ and CDAI, also the effect of combined therapy on HAQ and CDAI. According to age distribution; 37% at the age of 36-45yrs, 26.0% were in the age group 46-55 yrs, 16% in the age group 26-35 yrs, 14.0% were in the age group 15-25 yrs and 7.0% in the age group 56-65 yrs. Regarding the distribution in the study population according to gender; Male were 5 (5.0%) and females 95 (95.0%). Most study group was married 92 (92.0%), single were 7 (7.0%) and divorced were 1 (1.0%). According to which drug type is used: MTX 49 (49.0%), HCQ 71 (71.0%), LEFLU 6 (6%), Sulpha 2 (2.0%) and Azathio 3 (3.0%). HAQ showed minimal symptoms in 69 patients (69.0%), remission in 15 (15.0%), and moderate symptoms in 16 (16.0%). Moreover DMARD was initiated at the same time with the diagnosis in 64patients (64.0%) and other time in 36 patients (36.0%). The percentage of people using combined therapy was 26% and 74% was using mono therapy.

CDAI was compared between different the different drugs among study group and the results as follow: in MTX; low CDAI was found in the study group in 16 (32.7%) and followed by moderate in 15 (30.6%) patients, whereas the remission was only in one patient (2.0%). Regarding CDAI

and HCQ; Low CDAI was the most common indication in study group in 24 (33.8%) patients and followed by moderate were 21 (29.6%), high were 20 (28.2%) patients, and remission were 6 (8.5%). Also between CDAI and Sulfa of the study population; Moderate was one patient (50.0%), high were 1 (50.0%), and remission was 6 (8.5%) patients. Between CDAI and LEFLU of the study population: moderate 4 (66.7%), and high 2 (33.3%). On the other hand, AZA using study population showed Low, moderate and high CDAI; each of them individually was 1 (33.3%).

Moreover HAQ was compared between the different drugs in the study population. Firstly, MTX takers showed minimal in 32 people (65.3%) followed by moderate 12 (24.5%) and remission 5 (10.2%) people. According to HCQ; minimal were 48 (67.6%) followed by remission were 12 (16.9%) and moderate 11 (15.5%). LEFLU on the other hand causing minimal in 5 persons (83.3%) and moderate in one (16.7%). However SULPH users of the study population showed minimal and moderate only which each of them individually was 1 (50.0%). HAQ and AZA comparison showed only minimal with 3 patients (100.0%) but the difference was statistically not significant (P. value =0.322).

The association between CDAI and the different timing of initiation of DMARD showed mostly in moderate 23 (35.9%), followed by low 21 (32.8%), high were 13 (20.3%) and remission were 7 (10.9%). The difference was statistically not significant (P. value =0.023). The association between HAQ and difference of initiation of the DMARD of the study population: mostly low in 23 (70.3%), followed by remission in 12 (18.8%), and moderate in 7 (10.9%) patients and the difference was statistically not significant (P. value =0.036).

The relation between CDAI and the use of combined (MTX and HCQ) or single DMARD of the study population revealed mostly combined usage (71 people) and low CDAI was the dominant (24 persons), followed by moderate were 21 persons, high were 20 persons and remission were 6. The difference was statistically significant (P. value =0.001). lastly, regarding the association between HAQ and the use of combined and single DMARD of the study population, the combined population (71) mostly in low were 48, followed by remission were 12 (18.8%), and moderate were 11. The difference was statistically significant (P. value =0.004).

## 4. Discussion

In 100 adult Sudanese patients affected by rheumatoid arthritis using American college of rheumatology 2010 criteria were seen and studied in the period from Nov 2014 to Jan 2015 in the referred clinics of rheumatology –Omdurman Military Hospital, Al Ribat Hospital and Omdurman Teaching Hospital. The results of this study were compared to similar studies conducted elsewhere in the world.

The study showed that the major age distribution were in the third and sixth decay At the age of 36-45 was % 37 and the disease affect female more. Male were 5 (5.0%) and females 95 (95.0%). This is consistent with general fact that any age can be affected, mostly the third decade with female predominance [1]. The majority of patients in our study were married.

In the study the most commonly used DMARDs is Hydroxy Chloroquine (HCQ) then Methotrexate (MTX), Sulphasalazine (SULFA) is the least to be used. This is different to what have been said by Ryan, Lisa in May 1999 in the Current Opinion in Rheumatolog when published that Methotrexate is the most chosen drug [15] we need to investigate it more and it could be because of the age group affected and mostly female and married and the fear of the teratogenicity of Methotrexate.

About 36% were using combined Methotrexate and Hydroxyl Chloroquine and this is recommended by COBRA study where they studied 155 patients with early rheumatoid arthritis and gave them either monotherapy or combined therapy they found that patients received combined therapy had less radiologic progression compared with the monotherapy [16] but the majority of the patients in our study where using monotherapy, this could be due to the fear of the side effects as many rheumatologist prefer using monotherapy to decrease toxic effect of the DMARDs.

The highest percentage of patients shows minimal score of HAQ and almost similar percentage shows moderate and remission score in functional disability assessment for the studied patients having rheumatoid arthritis and taking DMARDs.

Regarding CDAI and the use of Methotrexate (MTX) the study shows that only one patient from the 49 patients; shows remission and patients have of low, moderate and high CDAI score respectively. Also the remission CDAI was only seen in 6 patients out of 71 patients taking Hydroxychloroquin (HCQ), again almost equal percentage of low, moderate and high CDAI in patient using HCQ no remission were found with SULPHA, LEFLU, AZA. (So to achieve remission there should be frequent measurement of disease activity similar to what has been said in (TICORA) study that giving DMARD and close monitoring induce remission [27] where they did a single blind study and patients were randomly assigned to routine outpatient care with conventional DMARDs and were followed up for a period of time remission was higher in the intensive care group.

The highest percentage of remission CDAI was seen in patients taking Hydroxychloroquine(HCQ) these finding support that using HCQ is best in achieving remission is the DMARD contradict that Methorexate is the best in achieving remission CDAI and most often chosen for initial treatment (Current Opinion in Rheumatology) [15].

Most patients using MTX show minimal functional disability (HAQ). Also most patients taking HCQ show minimal HAQ (TABLE8) the percentage of remission HAQ was higher with HCQ than MTX no remission seen with other DMARDs. Leflunamide showed 5 patients out of 6 taking it to have minimal HAQ score. In the two patients taking Sulpasalazine one showed minimal HAQ and the other showed moderate HAQ. However Azathioprine causes only minimal HAQ.

There are 36% who don't start DMARD at the same time of diagnosis but the majority which is 64% start it at the time of the diagnosis going with recent recommendation as early initiation is needed to affect disease activity and progression.

On studying the relation between HAQ and the difference in time of initiation of DMARD the p value was 0.036 the p value was not significant and this mean that starting DMARD early does not affect functional disability (HAQ) of patient with DMARD. This is not similar to what Borg and colleagues said when they studied 137 participants have early RA for less than 2 years they start treatment with Auranofin in one group and the other DMARDs they found that early treatment with DMARDs had produced greater improvement in physical function than delayed treatment [11].

Relation between CDAI and the time of initiation of DMARD show p value of 0.023 and it was not significant showing that early initiation of DMARD don't affect disease activity of rheumatoid arthritis (CDAI) also this is not similar to Borg and colleagues said [9,10,11] early treatment decrease disease activity.

In studying the relation of the use of combined DMARDs and it is effect on the HAQ and CDAI both showed significant p value this is similar to what had been said by COBRA study. As they studied 155 patients with early rheumatoid arthritis and gave them either monotherapy or combined therapy they found that patients received combined therapy had less radiologic progression compared with the monotherapy [16].

## 5. Conclusions

In conclusion, this is a study of DMARDs conducted in Sudanese population. It is found that the most commonly used DMARDs are MTX and HCQ Combination therapy is not widely used in our patients. Most of our patients show minimal functional disability assessed by HAQ. MTX and HCQ affect disease activity CDAI and functional disability almost the same. Our patients using MTX and HCQ show minimal score using HAQ small percentage show remission no remission with other type of DMARDs. Early initiation of DMARD is not important in the treatment of RA it affects functional disability and disease activity, combination therapy affect significantly functional disability assessed by HAQ and disease activity assessed by CDAI. More cohort studies with larger numbers of patients are needed.

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