THE ROLE OF HYDROXYCHLOROQUINE AS MONOTHERAPY IN MANAGING EARLY UNDIFFERENTIATED ARTHRITIS: A PROSPECTIVE HOSPITAL–BASED STUDY

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Abstract

Introduction: Early undifferentiated arthritis (EUA) is a common form of arthritis comprising, joint pain, stiffness and swelling with no definitive diagnosis. Patients of EUA can progress to other forms of rheumatic arthropathies such as rheumatoid arthritis or remain in the same form or spontaneously disappear. The main focus of this study is to explore the potential effect of hydroxychloroquine (HCQ) in management of EUA as a monotherapy treatment. **Methods:** This is a prospective hospital-based study which was conducted in Almwada hospital in Khartoum, Sudan. The study included thirty patients of EUA. Full clinical examination and history were done by a rheumatologist, and all the related investigations were obtained, and they all received HCQ after EUA diagnosis has been established.
Result: The study shows that 96% of the patients responded well to the treatment and 10% had their duration of treatment doubled to show a favorable response. We also found that female patients were more commonly affected than male ones with higher incidence among middle aged as compared to others. After treatment with HCQ, 86.6% of the patients showed average mean decrease in erythrocyte sedimentation rate (ESR) by 44%, the other 13.4%, even though they were symptoms free after treatment they showed increased level of ESR by 30% average. **Conclusion**: In the present study we found out most of the EUA patients are well responded to the HCQ treatment, and most of them respond from the first course of treatment, the study also shows higher incidence among female in compared to male.

Key words: Early undifferentiated arthritis, Middle age group, Hydroxychloroquine, Monotherapy.

Introduction

Early undifferentiated arthritis is an inflammatory polyarthritis or Monarthritis with no definitive diagnosis that has a duration of less than three months and do not categorized under any connective tissues or rheumatic disease (Combe et al., 2017; Dixon & Symmons, 2005; Wevers-de Boer, Heimans, Huizinga, & Allaart, 2013), patients with Early undifferentiated arthritis minimally should have one tender joint or swelling (Aletaha et al., 2010), EUA can be initial presentations of many rheumatic diseases including rheumatoid arthritis(Combe et al., 2017; Dixon & Symmons, 2005; Vaidya, Baral, & Nakarmi, 2018). After the 2010 EULAR/ACR updated the classification criteria (Aletaha et al., 2010) many cases of EUA can be diagnosed as early rheumatoid arthritis (ERA). Many patients of early scleroderma, rheumatoid arthritis or lupus are presented as EUA and their diagnosis becomes more obvious after a period of one year and sometimes months (Suresh, 2004), about one third of EUA patients will achieved spontaneous remission(Stockman et al., 2006), a third will remain as EUA and the rest will progress to rheumatoid arthritis (RA)(Hazes & Luime, 2011).

There is no standard management for EUA, most of the treatments are off-label such as steroids or non-steroids anti-inflammatory drugs, until the patient exhibited apparent features of chronicity then others alternative drugs like Disease Modifying Anti Rheumatic Drugs (DMARDs) are used(van Dongen et al., 2007). Current evidence proved that it is unjustifiable to wait until erosions or chronicity to initiate DMARDs (Bosello et al., 2011; Joshua, Edmonds, & Lassere, 2006; Sudol-Szopinska et al., 2013), and the goal of management is to reduce the risk of chronicity and complications of the disease (Combe et al., 2017; Smolen et al., 2016), if the patient doesn't reach significant improvement, then the therapeutic agent is upgraded as needed in a form of combination of methotrexate, hydroxychloroquine and sulfasalazine with DMERDs according to the patient tolerance and side effect profile, In spite of the efforts and the studies on EUA, until now no clear pathophysiology has been identified.

The current study aims to explore the effectiveness of using hydroxychloroquine as monotherapy for treatment of EUA patients.

Methods

This is a hospital-based study which was conducted in Almwada hospital, Khartoum, Sudan, where we screened and selected Prospectively a number of 30 patients according to specific criteria in the outpatient department of medicine in the period of April 2017- April 2018. All patients have been examined (Musculoskeletal examination) with detailed history taken by specialist (Dr. Ziryab Imad Taha Mahmoud) to achieve the final result after reviewing the lab investigation.

The study is focusing on the effect of hydroxychloroquine (HCQ) on undifferentiated arthritis patients after fulfill the inclusion criteria which includes only patients regardless of the age and gender, complaining of multiple tender joint pain in duration lees than six weeks , and the exclusion criteria is patients complaining of joints pain associated with any of the following: swelling, stiffness, deformity, fever, duration more than six weeks, any other systemic symptoms. We collected the data from the patients and they were given a discharge summary card for their regular follow up, the card contains the date of every follow up meeting for checkup of the Renal function test, ESR level and general well-being, the initial clinical presentation, all the relevant investigation such as the ESR, rheumatoid factor (RF), anti-Cyclic Citrullinated Peptide (Anti CCP), Antinuclear antibodies (ANAs), Blood Urea (BU), Serum Creatinine, Liver enzymes and bilirubin level, Complete Blood Count (CBC), and urine microscopic examination. Finding of the clinical examining, duration of the disease, medication patterns, assessment various organs involvement, gender, age, ethnic and geographical distribution, were also been recorded to include in data sheet.

Modified Disease Activity Score 28 (DAS28), is being used to establish the diagnosis and the treatment outcome. The therapeutic approach was initiated by using the HCQ as monotherapyin management of EUA at a dose of 400 mg daily, divided twice, in tablet form, for a period of 3 months, and another three months in the cases where a poor was noticed according to DAS28 criteria.

Analysis

The collected data were stored using the computer program. Nominal data are expressed as frequency or proportion. All statistical analysis was performed using the Statistical Analysis Package for Social Science (SPSS, v.22.0 Chicago, Illinois, USA), an independent T test and one-way ANOVA are tested with a level of the significant set at ($P<0.05$) .

Results

In this study we found that female has the higher prevalence among our patients in a percentage of 86.7% and male patients represented the remaining 13.3 % (fig 1). Regarding age group, we classified the patients into three categories, age 20 years and less than 40years, 40 to less than 60 and 60-80years (Table 1). The middle age group patients which are between 40- 59 years are the most affected group (46.7%), followed by 36.7% for the group between 20 years and less than 40 years, and the last age group which is the group between 60-80 years represent the remaining 16.7% (Table 1). Further analysis showed that response to treatment is 96.7%, while the remaining 3.3% of the patients shows no treatment response (Fig2). Also, we noted that 90% of the patients were responsive to treatment from the first course which is 3 month, while the other 10% had their duration of treatment doubled (Fig 3). Regarding the treatment effect on erythrocyte sedimentation test (ESR), they were categorized into three groups, 86.6% of the patients had their average mean decreased to 44% after they receiving the treatment, 3.3% of the patients had their ESR decreased to 13% after the treatment, the remaining 13.4% of the patients showed increase in ESR level by 30% even after treatment but their complains disappeared (Fig 4).

The std deviation of the age and sex are 0.71 and 0.34 respectively (Fig 5), the age groups, ESR, gender, duration and treatment dosage, clinical presentation, outcome and investigations all have been showed in Table (2). The initial DAS28 of the patients at the time of diagnosis shows that 73.3% of the patients has a high score and 26.7% with moderate score, after receiving treatment with HCQ for three months, the high score group had 50% lower DAS28 score and 45.4% of them became moderate score and 4.6% achieved total remission. Among those 45.4% with moderate DAS 28 score after receiving three months treatment, 20% of them received another three months treatment and achieved 100% remission. The second group with moderate DAS28 at the time of diagnosis after three months of treatment also showed 50% lower score, 37.5% remission and the remainder 12.5% showed no decrease in DAS28 score until they received another three months treatment to end by having 100% remission (Fig 6) (Table3).

According to Sheer's equation results showed that the mean size of ZrO_2 nanoparticles molecules under study were 29.8 nanometers. The results were compared with (Vasaikar et al., 2017). They showed that the size of the particles (20 nanometers) when measured according to the Shearer equation and the highest value of the X-ray oxides measured by XRD. While (Arefian et al., 2015) the XRD value of ZrO_2 was 35 nanometers. The XRD measurement is used to identify the crystallization of molecules. In some cases, the crystallization of these molecules is not perfect, due to the insufficient thermal processor and time during the preparation process.

The results of X-ray diffraction analysis show the crystallization or calcification of zirconium, and the removal of the protein improves the biopolymerization of zirconium (Haghi et al., 2012). It is also used to detect the nature of particulate matter.(Gowri, Gandhi and Sundrarajan., 2014) The results of this study showed that the molecules of zinc oxide have a crystalline nature.

Table 1: Socio-demographic variables and response to treatment

Variables	No.	(%)	P-value
Gender			
Male	4	13.3%	<0.05
Female	26	86.7%	
Total	30		
Age groups (years)			
20-39	11	36.7%	<0.05
39-60	14	46.7%	
60-80	4	16.7%	
Response to treatment			
Responded	29	96.7%	<0.05
Not responded	1	3.3%	

Table 2: Patients variation age, gender, treatment duration, clinical presentation and clinical investigations

Age	Baseline ESR	Gender	Duration Of Treatment	Course of Treatment	Clinical Presentation	Outcome	ESR After 3 Months From Treatment	ACCP, UG ANA, RFT LFT, CBC
60	55	Female	3 months	1	tender multiple Joint pain	Not responded	86	Non-significant
45	25	Female	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
42	25	Female	3 Months	1	tender multiple Joint pain	Responded	26	Non-significant
50	75	Male	3 Months	1	tender multiple Joint pain	Responded	35	Non-significant
36	52	Male	3 Months	1	tender multiple Joint pain	Responded	45	Non-significant
40	75	Female	3 Months	1	tender multiple Joint pain	Responded	45	Non-significant
30	75	Female	3 Months	1	tender multiple Joint pain	Responded	60	Non-significant
70	70	Female	3 Months	1	tender multiple Joint pain	Responded	55	Non-significant
55	60	Male	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
38	35	Female	6 Months	2	tender multiple Joint pain	Responded	25/20	Non-significant
45	25	Male	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
37	75	Female	3 Months	1	tender multiple Joint pain	Responded	50	Non-significant
22	65	Female	3 Months	1	tender multiple Joint pain	Responded	55	Non-significant
50	55	Female	3 Months	1	tender multiple Joint pain	Responded	40	Non-significant
40	50	Female	3 Months	1	tender multiple Joint pain	Responded	40	Non-significant
39	75	Female	3 Months	1	tender multiple Joint pain	Responded	65	Non-significant
55	75	Female	3 Months	1	tender multiple Joint pain	Responded	65	Non-significant
42	62	Female	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
39	50	Female	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
60	55	Female	6 Months	2	tender multiple Joint pain	Responded	48/30	Non-significant
40	30	Female	3 Months	1	tender multiple Joint pain	Responded	10	Non-significant
27	65	Female	3 Months	1	tender multiple Joint pain	Responded	40	Non-significant
35	55	Female	3 Months	1	tender multiple Joint pain	Responded	35	Non-significant
60	30	Female	3 Months	1	tender multiple Joint pain	Responded	15	Non-significant
25	20	Female	3 Months	1	tender multiple Joint pain	Responded	5	Non-significant
30	70	Female	3 Months	1	tender multiple Joint pain	Responded	20	Non-significant
44	60	Female	3 Months	1	tender multiple Joint pain	Responded	40	Non-significant
80	70	Female	3 Months	1	tender multiple Joint pain	Responded	30	Non-significant
50	60	Female	6 Months	2	tender multiple Joint pain	Responded	40/10	Non-significant
40	60	Female	3 Months	1	tender multiple Joint pain	Responded	40	Non-significant

Table 3: DAS28 score of the patients at the time of diagnosis and after treatment.

No	Initial DAS28	Severity	DAS28 after three months treatment	Severity	DAS28 after six months treatment	Severity
1	4.6	Moderate	2.8	Low	-	-
2	4.6	Moderate	2.84	Low	-	-
3	5.1	High	3.6	Moderate	-	-
4	5.7	High	3.05	Low	-	-
5	5.1	High	3.2	Moderate	-	-
6	5.3	High	3.2	Moderate	-	-
7	5.3	High	3.5	Moderate	-	-
8	5.4	High	2.8	Low	-	-
9	5.2	High	2.8	Low	-	-
10	4.9	Moderate	4.7	Moderate	2.1	Remission
11	4.6	Moderate	2.8	Low	-	-
12	5.6	High	3.3	Moderate	-	-
13	5.6	High	3.5	Moderate	-	-
14	5.51	High	3.2	Moderate	-	-
15	5.3	High	3.14	Low	-	-
16	5.8	High	3.6	Moderate	-	-
17	5.2	High	2.8	Low	-	-
18	5.09	Moderate	2.8	Low	-	-
19	5.16	High	5.09	Moderate	2.38	Remission
20	4.7	Moderate	1,16	Remission	-	-
21	5.27	High	3	Low	-	-
22	5.16	High	2.9	Low	-	-
23	4.59	Moderate	1.9	Remission	-	-
24	4.3	Moderate	1.3	Remission	-	-
25	5.6	High	2.1	Remission	-	-
26	5.22	High	3.14	Low	-	-
27	5.78	High	2.8	Low	-	-
28	5.22	High	4.9	Moderate	1.6	Remission
29	5.22	High	3	low	-	-
30	5.12	High	2.96	low	-	-

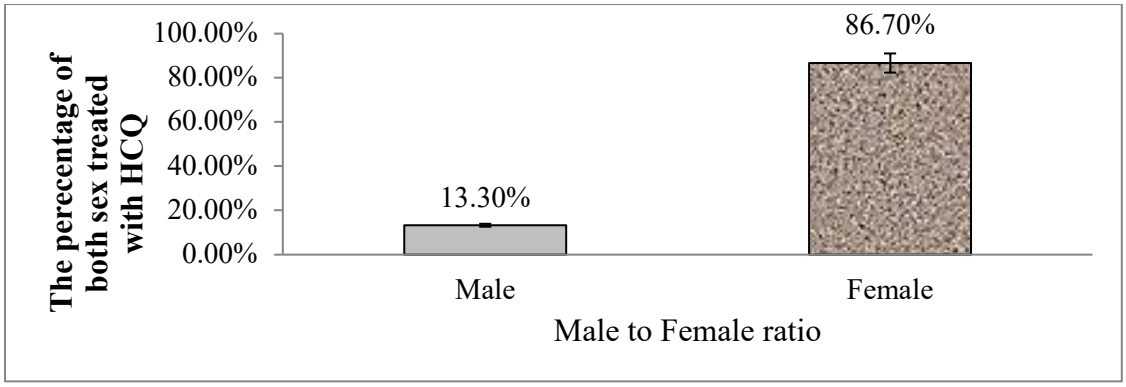

Figure 1: Demonstrates male to female ratio

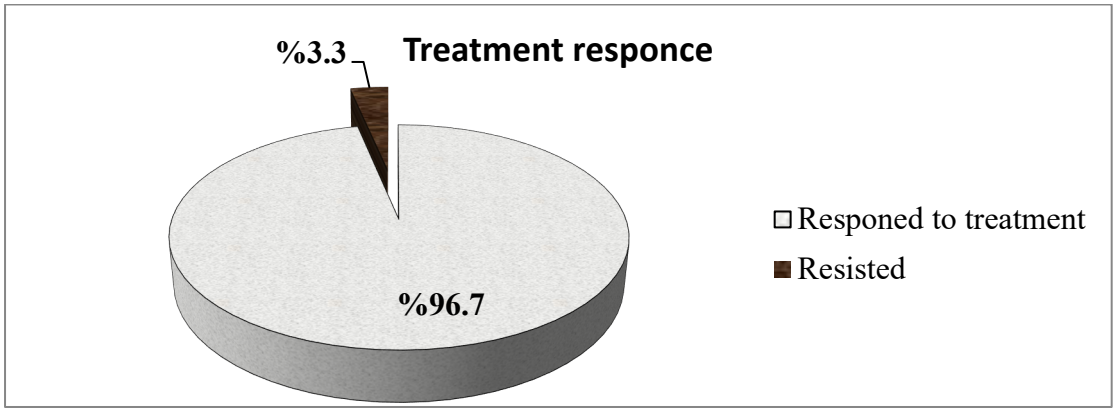

Figure 2: Patients response to the treatment

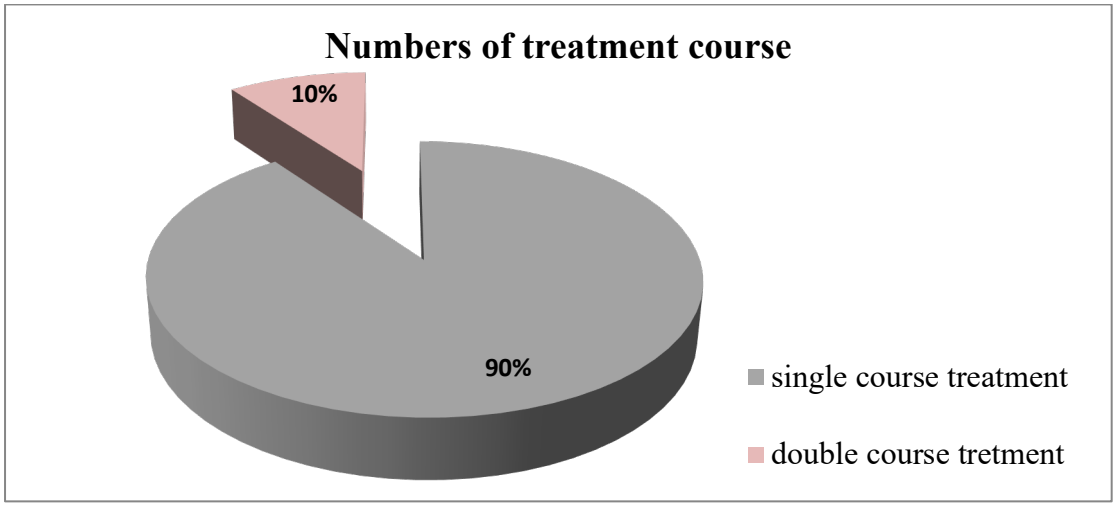

Figure 3: Patients response to the treatment

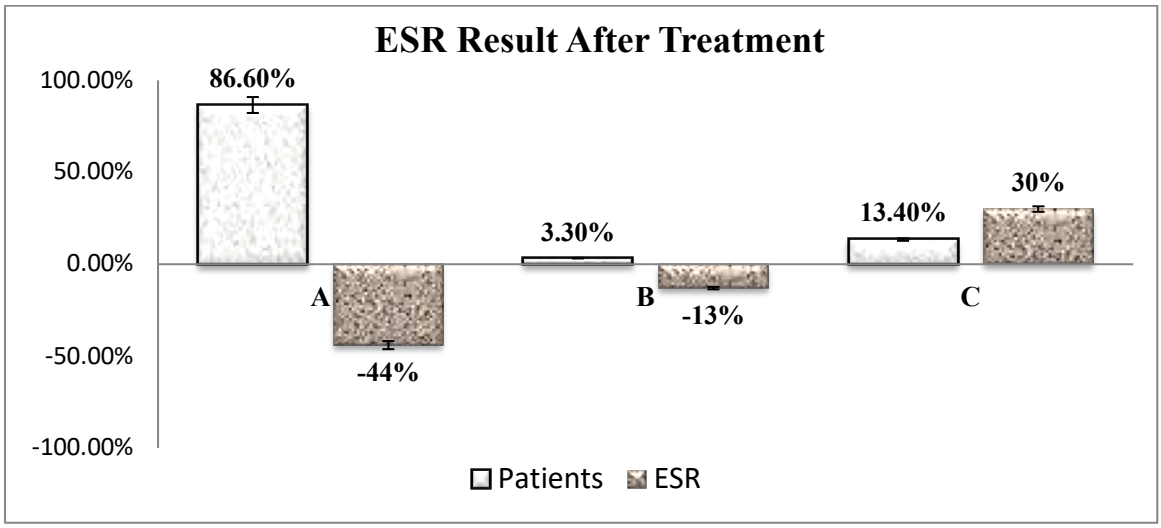

Figure 4: The average mean of the ESR after treatment

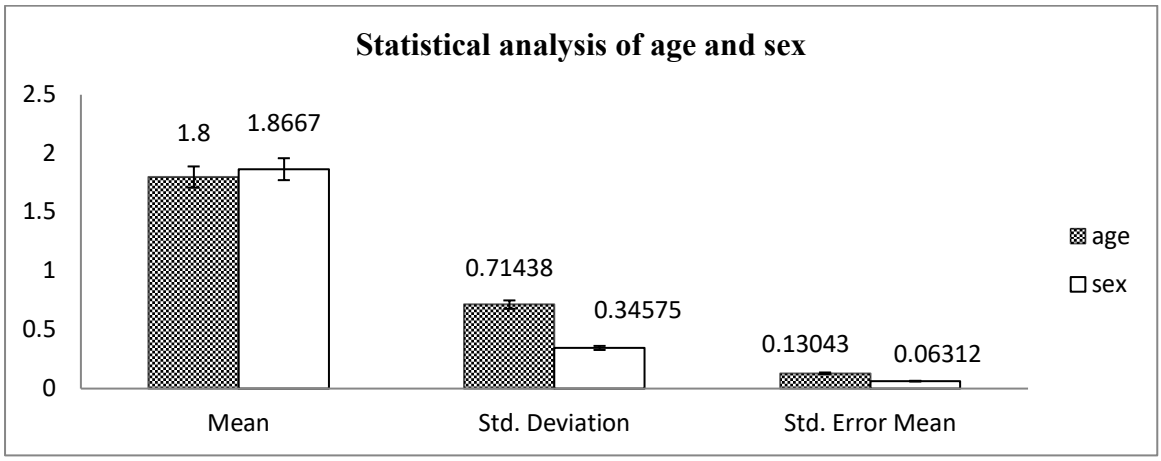

Figure 5: Age and sex statistics

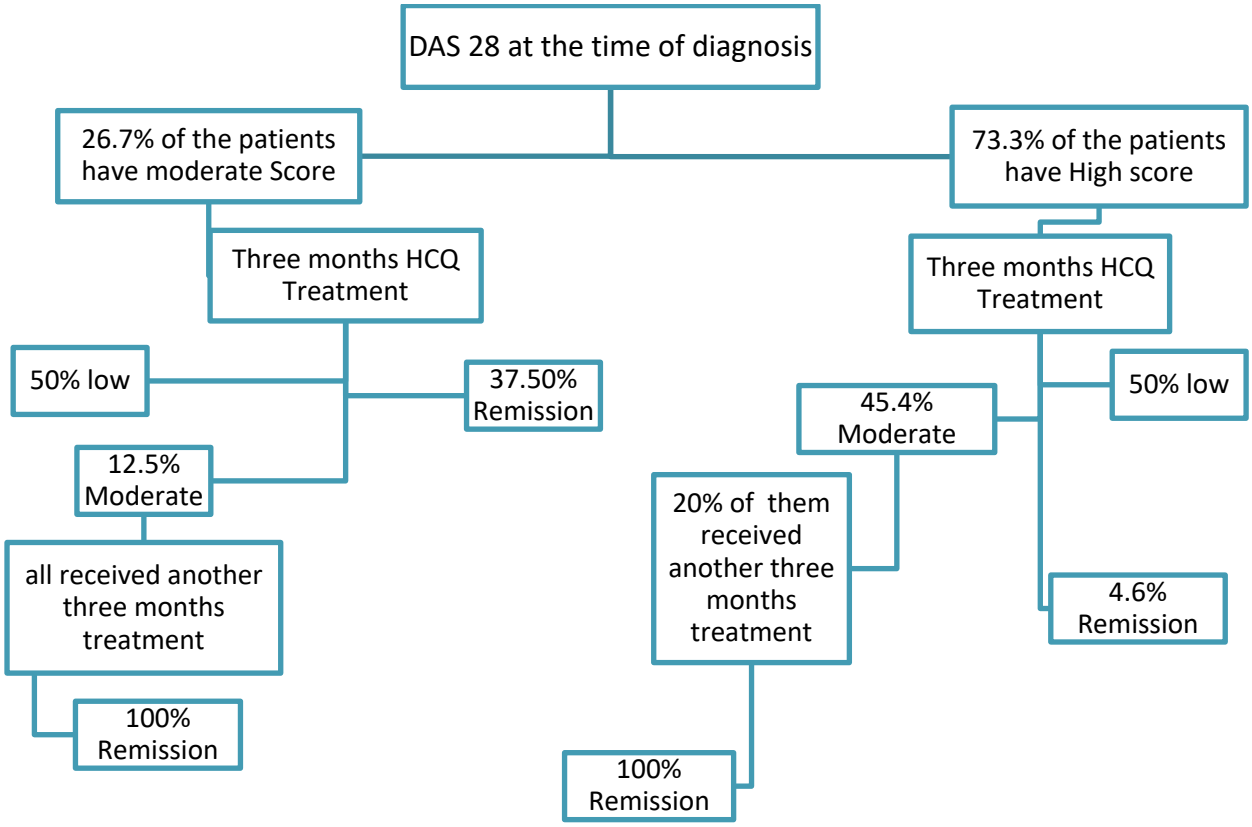

Figure 6: Modified DAS28 score percentage of the patients before and after treatment

Discussion:

This study is the first of its kind to explore the use of HCQ as a monotherapy in treatment of EUA in Sudan. Many studies have shown that vast majority of EUA are self-limiting especially those of viral etiology (Cacoub et al., 1999; Dendooven et al., 2006). We only focused on using HCQ and no other drugs for treatment of EUA. HCQ is an anti-malarial drug used in combination with other drugs to treat a wide variety of rheumatologic diseases such as systemic lupus erythematosus (SLE)(Spinelli et al., 2018), RA(Schapink, van den Ende, Gevers, van Ede, & den Broeder, 2019), primary Sjogren's syndrome (Wang, Zhang, Wei, & Hua, 2017) and Osteoarthritis (Lee et al., 2018), and until now its therapeutic potential and pharmacokinetic has not been identified and explored in depth (Hanaoka, Iida, Kiyokawa, Takakuwa, & Kawahata, 2019), Records show no studies regarding the use and efficacy of HCQ as monotherapy in EUA as the drug carry less side effect and complications compared to other drugs used in treatment of the same disease such as methotrexate which has a negative impact on the bone marrow (Yuncu, Bukucu, Bayat, Sencar, & Tarakcioglu, 2015) and Gastro intestinal system (Attar, 2010). Biologic treatment has less side effects with good outcome (Zavvar et al., 2019) but as most of the patients from the developing centuries have no affordability for the treatment and its need for regular follow up, HCQ provides a better option.

Regarding male to female ratio there are only few studies that estimated the sex difference in EUA, they also carry similar findings of this study as all of them showed that female constituted more than two thirds of total EUA patients (*O16 Aetiology of early undifferentiated arthritis in India*, 2009; Shankar S, 2010), no clear explanation have been identified yet but as EUA is an immunological disease (Foocharoen, Nanagara, Suwannaroj, & Mahakkanukrauh, 2011), recent evidence suggest that female hormones such as estrogen have strong role in development of autoimmune diseases(Somers & Richardson, 2014).

The study shows patients at the age of forties and fifties are the most commonly affected by the disease, the findings are directly in line with previous result with same sample size of this study (Shankar S, 2010), it remains unclear why exactly the middle age people are

more likely to be affected rather than those at old age who tend to be vulnerable due to their weak immune system(Merani, Pawelec, Kuchel, & McElhaney, 2017), but we postulate that this might be due to female sex hormones(Marder, Vinet, & Somers, 2015; Somers & Richardson, 2014) and also the menopausal change occured at this age (Su & Freeman, 2009).

The management of EUA is controversy as no standard treatment protocol is present, and around 30-60% of all the patients of EUA has self-limiting disease(Olivieri et al., 2012), so many questions been asked by us. Should we treat every patient? However, our primary focus was on the effectively of HCQ alone in the treatment of EUA and deliver significantly good result with 96.7% fully response, no comparable studies have been found in the literature neither an explanation.

DAS 28 score classify patient's well-being into three categories, high for those who score above 5.1, moderate for the patients who score between 5.1 and more than 3.2, low between 3.2 and more than 2.6, remission for and 2.6.and below. The score calculation depends on the number of joints involved, swelling of the joints, the global health assessment of the patient, and either the CRP or ESR (van Riel & Renskers, 2016). Half of the patients who received three months HCQ treatment with high score DAS28 their score turned to low, the other half had complete remission or became moderate. Those with six months duration of treatment their outcome ended by complete remission. As the used calculating score is modified to EUA patients, no available reviews or similar study were founded with same result, and no clear explanation has found

The limitation of this study is the sample size which is relatively low, early undifferentiated arthritis is not widely common, another limitation is the lack of the long term follow up for the patients to explore the total efficacy of the management and whether there is any recurrence of the previous complains and this lack of follow up is strongly due to patients factor as most of them were from rural and remote areas so establishing continuous communication with them somewhat is difficult.

Conclusion

In conclusion, this study investigated the efficiency of HCQ as monotherapeutic agent in treatment of early undifferentiated arthritis. Although extensive studies have not been conduct in this matter, substantial evidence about the role HCQ in rheumatologic diseases is already proved. 96.7% of the patients were completely cured and 90% of them responded from the first course of treatment. Female are commonly affected by the disease and the age group from 40 to less than 60 have the higher incidence.

Ethical approval and consent to publish

Obtained from federal ministry of health (FMOH), Khartoum, Sudan.

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