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Efficacy of Hydroxychloroquine in Rheumatic Diseases and Associated Co- morbidities

Eman Ahmed Hamed Omran[1], Safaa A. Mahran[1], Mohamed G. A. Saleh[2], Mohamed Salem Hareedy[3], Helal F. Hetta[4], Nesreen I. Ibrahim*[1], Manal Hassanien[1]

Departments of [1]Rheumatology and Rehabilitation, [2]Ophthalmology, [3]Pharmacology and [4]Medical Microbiology and Immunology, Assiut University, Assiut, Egypt

***Corresponding Author:** Nesreen I. Ibrahim, **Mobile:** (+20)1096594921, **Email:** nesreen.ismail1988@gmail.com

ABSTRACT

Background In the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), the antimalarial drug hydroxychloroquine (HCQ) is frequently used. It reduces the risk of illness flare-ups, prevents thrombosis, and lowers the possibility of long-term organ damage. HCQ's advantageous impact on cholesterol levels and diabetes risk reduction.

Objective: The aim of the present study was to identify the efficacy of HCQ in rheumatic diseases and associated comorbidities.

Patients and method: This cross-sectional study included a total of 71 RA and 9 SLE patients, attending at Department of Rheumatology, Rehabilitation and Physical Medicine, Assiut University Hospitals. University Hospitals. All patients subjected to complete history taking including medication history [HCQ dose (daily, cumulative) and duration], clinical examination, disease activity of RA was defined by DAS 28 (Disease activity scale) and disease activity of SLE by SELDAI-2K (Systemic Lupus Erythematosus Disease Activity Index). Laboratory assessments were performed including: routine investigation, autoantibodies

Results: HCQ has a role in control diabetes mellitus (DM) of our diabetic patients and had role in reducing the risk for atherosclerosis and a significant reduction in the lipid profiles as well as AI has been observed.

Conclusion: It could be concluded that HCQ is associated with a reduced risk of rheumatic diseases and its associated comorbidities.

Keywords: Systemic lupus erythematosus, Antimalarial drugs, DM, HCQ.

INTRODUCTION

Disease-modifying antirheumatic medicines (DMARDs), which include the antimalarial medications hydroxychloroquine and chloroquine, were accidentally and irrationally introduced to treat a variety of rheumatic diseases [(1)]. Hydroxychloroquine (HCQ) is the go-to medication for inflammatory rheumatic disorders like SLE, rheumatoid arthritis (RA), and others [(2)]. They have recently been proposed as a form of treatment for COVID-19 sufferers [(3)].

HCQ has been shown to decrease SLE activity and increase damage-free survival [(4)], improves target organ damage and survival in SLE patients [(5)]. Although some studies have suggested that HCQ therapy for SLE patients may have cardiovascular beneficial effects, other studies have failed to show any significant effect of HCQ on cardiovascular disease (CVD) [(6)]. HCQ could reduce disease activity of preeclampsia and may play a protective function to avoid SLE flare-ups during pregnancy, fetal growth restriction, and prematurity [(7)]. HCQ has also some metabolic effects by lowering fasting glucose, protection against diabetes, and improvement of the lipids profile [(8)]. HCQ has been demonstrated to improve clinical and laboratory results in RA, especially in moderate and early disease, even though it had no protective effect on radiographic progression. Most of the effects, such as an improvement in lipid profile and insulin resistance, are comparable to those felt by lupus patients [(9)].

The aim of the present study was to identify the efficacy of HCQ in rheumatic diseases and associated comorbidities.

PATIENTS AND METHODS

This cross-sectional study included a total of 71 RA and 9 SLE patients, attending at Department of Rheumatology, Rehabilitation and Physical Medicine, Assiut University Hospitals. University Hospitals.

Patients were 72 females and 8 males. Their average age was (48.2 ± 10.9) ranged from 20 to 75 years. All RA patients were diagnosed and fulfilled 2010 ACR/EULAR classification criteria for RA [(10)]. All SLE patients were diagnosed and fulfilled SLICC classification criteria for SLE [(11)].

Inclusion criteria: Adult rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients who received HCQ treatment.

Exclusion criteria: Patients < 18 years, individuals experiencing renal failure (creatinine clearance ≤ 30 ml/min), patients with ocular disorders include glaucoma, hereditary fundus dystrophies, dense media opacity preventing fundus visibility, optic neuritis, and uveitis that may cause anomalies in screening tests used to detect HCQ toxicity.

***Ethical Consideration*:**

This study was ethically approved by Academic and Ethical Committee at Assiut University (No. 17200029). Written informed consent of all the participants was obtained. The study protocol

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conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

The participants were subjected to the following:

A) Full history taking including:

- Age, Sex, disease duration (years), duration of morning stiffness (hours), presence of any deformity, extra articular manifestations, diabetes mellitus, smoking, hypertension, dyslipidemia.
- Current medications in the form of:
  - HCQ dose and duration including:
    1- Daily dose/actual body weight (also known as actual body weight (ABW), body weight (BW), or simply standardized weight) is the measurement obtained using a calibrated scale when the person is able to stand unaided.
    2- Daily dose/ideal body wt (The Ideal Weight Calculator computes ideal body weight (IBW) ranges based on height, gender, and age).
    Men: IBW (kgs) = 22 × (height in meters)^2.
    Women: IBW (kgs) = 22 × (height in meters − 10 cm)^2.
    3- Cumulative dose/actual body wt. (online calculator).
    4- Cumulative dose/ideal body wt.
  - DMARD as monotherapy or combination therapy.
  - Non-steroidal anti-inflammatory drugs (NSAIDs).
  - Steroid use (local or systemic) including dose and duration.
  - Biological treatment.
  - Other medications.
- Height and weight were measured, and body mass index (BMI) was calculated as weight (kg)/ height (m)^2 (kg/m^2) and were assigned to either class [12].
- Underweight: BMI 18.5 kg/m^2.
- A BMI between 18.5 to 24.9 kg/m^2 is considered normal or excellent.
- Overweight: a BMI of 25 to 29.9 kg/m^2 or higher.
- Obese: BMI greater than 30 kg/m^2.

B) Clinical examination: Through clinical examination and eye examination**.**

Disease activity indices:

Disease activity of RA cases was assessed using the Disease Activity Score (DAS28) based on:

- Number of swollen joints (SJ), and the number of sensitive joints (TJ) (Assessing 28 joints which include 10 PIPs (proximal inter phalangeal) joints, 10 MCPs (metacarp-phalangeal) joints, 2 wrists, 2 elbows, 2 shoulders, and 2 knees joints).
- Erythrocyte sedimentation rate (ESR) mm/hour.
- The assessment of their general health using a VAS of 100 mm yielded a score for their global health (GH).

- Mobile application was used to calculate DAS 28.

Where:

- Remission was recorded when DAS28 was ≤ 2.6.
- Low disease activity was recorded when DAS28 was (>2.6 to ≤ 3.2).
- Moderate disease activity was recorded when DAS28 was (>3.2 to ≤ 5.1).
- High disease activity was recorded when DAS28 was (> 5.1) [13]**.**

- **Disease activity of SLE cases was assessed using SLEDAI-2 K (c-SLEDAI-2 K):**
  - **Active disease** defined as a c-SLEDAI-2 K score ≥ 6.
  - **Inactive disease** is < 6 in SLEDAI-2 K score [14].

C) Laboratory investigations:

1. **Routine investigations:** Complete blood count (CBC), first hour ESR, liver and kidney function tests (aspartate transaminase (AST), alanine transaminase (ALT), serum bilirubin , BUN, serum creatinine were done on auto-analyzer BM/Hitachi 911 (Boehringer Mannheim, Germany).
2. **Autoantibodies:**
   - RF (Rheumatoid factor): Measured by serum latex agglutination test in (IU/mL) (N: < 8 IU/mL).
   - ANAs (Anti-nuclear antibody) by qualitative enzyme linked immunosorbent assay (ELISA).
   - Anti-dsDNA (double stranded DNA) antibodies levels using ELISA kit measured in mg/dl (N: 0.6-1.2 mg/dl).

Statistical Analysis

The data was collected and examined using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York, 2015). Continuous data was expressed as mean SD or median and interquartile range, whereas nominal data was expressed as frequency (percentage).

The study's Chi2-test was used to compare the nominal data of the different groups, while the genotyping frequencies, minimal allele frequencies (MAF), and p values of Hardy-Weinberg equilibrium (HWE), the p values of either conventional one-way ANOVA (for normal data) or Kruskal-Wallis (for data did not pass the normality test), the p values of either Chi-square or Fisher exact test, and the P values for the number of SLE patients are shown.

RESULTS

Demographic data of the studied population:

Table 1 shows baseline socio-demographic and clinical data of patients. Eighty patients were included in the study, 72 (90%) were females, 8 (10%) were males. Their average age was (48.2 ± 10.9) ranged from 20 to 75 years. Also, 29 (36.3%) were smokers, 45 (56.3%) were hypertensive, 24 (30%) were diabetics and the mean BMI was 27.1 ± 3.8. Additionally, most cases had RA (89%) and the minority had SLE (11%).

Table (1): Baseline Socio-Demographic and Disease History of Study group

Parameter		n = 80
Age (years)	**Mean ± SD**	48.23 ± 10.9
	Median (IQR)	49 (20 - 75)
Sex	**Female**	72 (90%)
	Male	8 (10%)
Residence	**Asyut**	70 (87.5%)
	Outside Asyut	10 (12.5%)
Occupation	**Housewife**	71 (88.8%)
	Employed	9 (11.2%)
Marital Status	**Married**	57 (71.2%)
	Unmarried	23 (28.8%)
Smoking Status	**Smoker**	29 (36.3%)
	Non-smoker	51 (63.7%)
BMI (kg/m^2)	**Mean ± SD**	27.13 ± 3.8
	Median (IQR)	26.5 (20 - 40)
BMI Category	**Normal**	17 (21.2%)
	Overweight	47 (58.7%)
	Obese	16 (20.1%)
Comorbidity	**DM**	24 (30%)
	HTN	45 (56.3%)
Disease Category	**RA**	71 (88.8%)
	SLE	8 (11.2%)

SD=Standard Deviation, IQR=Interquartile Range, BMI=Body Mass Index, DM=Diabetes Mellitus, HTN= Hypertension, RA=Rheumatoid Arthritis, SLE=Systemic Lupus Erythematosus

Clinical characteristics of the study group:

Table 2 summarizes the clinical characteristic of the studied group. The mean disease duration for patients was 11.4 ± 6.4 years. Further, about 81% (n=65) of patients had morning stiffness with a mean duration of 0.64 ± 0.12 hour.

Also, about three-quarters (73.8%) had hand swelling versus about two-thirds (61.3%) had knee swelling. Moreover, about three-quarters (76.3%) of patients had deformity among those (73.7%) had toes deformity and (52.6%) had hand deformity.

Table 2 also shows the clinical manifestations of the studied cohort. Regarding Extra-articular manifestations: about three-quarter (74%) patients had extra-articular manifestations; of whom 41.9% had SCN, 40.5% had xerophthalmia, 33.8% had blurring of vision and 32.4% had xerostomia. About half of cases (51.3%) had sleep disturbance. As regards constitutional manifestation: nearly one-third (33.8%) of patients had fever, 75% had fatigue and 62.5% had malaise.

Table (2): Clinical Characteristics of Study group

Parameter		n = 80
Disease Duration/years	**Mean ± SD**	11.4 ± 6.4
	Median (IQR)	10 (2 - 30)
Morning Stiffness	**Yes**	65 (81.2%)
	No	15 (18.8%)
Stiffness-Duration (hours) (n=65)	**Mean ± SD**	0.64 ± 0.12
	Median (IQR)	0.5 (0.25 – 1.0)
Swelling Site	**Wrist**	73 (91.3%)
	Knee	49 (61.3%)
	Ankle	43 (53.8%)
	Elbow	26 (32.5%)
	Others	10 (12.5%)
Deformity	**No**	61 (76.3%)
	Yes	19 (23.7%)
Deformity Site (n=19)	**Toe**	14 (73.7%)
	Wrist	13 (68.4%)
	Finger	7 (36.8%)
	Ankle	2 (10.5%)
ROM	**Free**	52 (65%)
	Limited	28 (35%)
Extra-articular Manifestations	**Yes**	74 (3.8%)
	Subcutaneous Nodule	31 (41.9%)
	Xerophthalmia	30 (40.5%)
	Blurring of Vision	25 (33.8%)
	Xerostomia	24 (32.4%)
	Photosensitivity	8(11.2%)
	Others	18 (24.3%)
Associated Symptoms	**Sleep Disturbance**	41 (51.3%)
	Fever	27 (33.8%)
	Fatigue	60 (75%)
	Malaise	50 (62.5%)
	Weight Loss	22 (27.5%)
	Night Sweat	3 (3.8%)

SD=Standard Deviation, IQR=Interquartile Range, ROM=Range of Motion

Medication history of the studied groups:

Therapeutic history of studied patients was illustrated in **Table 3.** Mean of MTX duration was 15.1 ± 2.9 years where the mean of HCQ duration was 7.7 ± 4.3 years.

Table (3): Medication history of Study group

Parameter		n = 80
MTX Duration/ years (n=62)	**Mean ± SD**	15.08 ± 2.9
	Median (IQR)	15 (12.5 - 25)
MTX Dose (n=62)	**Mean ± SD**	2.66 ± 0.3
	Median (IQR)	2 (1 - 10)
HCQ Duration/ years	**Mean ± SD**	7.74 ± 4.3
	Median (IQR)	7 (2 – 23)
HCQ Duration Category	**< 5 years**	18 (22.5%)
	> 5 years	62 (77.5%)
HCQ Daily Dose/Weight		
Actual Body Weight	**< 5 mg/kg**	18 (22.5%)
	> 5 mg/kg	62 (77.5%)
Ideal Body Weight	**< 6.5 mg/kg**	38 (47.5%)
	> 6.5 mg/kg	42 (52.5%)
Cumulative HCQ Dose/weight (g/kg)		
Actual Body Weight	**Mean ± SD**	4.3.4 ± 1.01
	Median (IQR)	3.8 (1 – 14.1)
Ideal Body Weight	**Mean ± SD**	5.1 ± 1.10
	Median (IQR)	4.8 (1.1 – 14.8)
Steroid Duration/ years (n=53)	**Mean ± SD**	4.74 ± 3.9
	Median (IQR)	4 (1 - 20)
Steroid Dose (n=53)	**Mean ± SD**	11.70 ± 2.32
	Median (IQR)	10 (5 - 60)
Steroid Dose Category	**Low Dose (< 7.5 mg)**	22 (27.5%)
	Medium Dose (7.5-30 mg)	50 (62.5%)
	High Dose (30-<100 mg)	8 (10%)

SD=Standard Deviation, IQR=Interquartile Range, MTX=Methotrexate, HCQ=Hydroxychloroquine

Table 4 demonstrates the different disease activity of study group. For the RA group, swollen 28 joints had a mean of 4.93 ± 0.91, tenderness 28 had a mean of 7.77 ± 1.6 and DAS-28 had a mean of 4.19 ± 0.84.

For the DAS-28 category; about one-third (32.4%) had high activity, about 40% had moderate activity while about 28% were in remission. For the SLE group, about one-third (32.4%) had no flare, about 56% had mild/moderate flare and about 11% had severe flare.

Table (4): Disease Activity of Study group

RA Group		n = 71
Swollen 28	● **Mean ± SD**	4.93 ± 0.91
	● **Median (IQR)**	2 (0 - 21)
Tenderness 28	● **Mean ± SD**	7.77 ± 1.6
	● **Median (IQR)**	5 (0 - 25)
DAS 28	● **Mean ± SD**	4.19 ± 0.84
	● **Median (IQR)**	4.25 (1.7 – 7.3)
DAS Category	● **High Activity**	23 (32.4%)
	● **Moderate/Low Activity**	28 (39.4%)
	● **Remission**	20 (28.2%)
SLE Group		**n = 9**
SLEDAI-2k	● **No Flare**	3 (33.3%)
	● **Mild/Moderate Flare**	5 (55.6%)
	● **Severe Flare**	1 (11.1%)

SD=Standard Deviation, IQR=Interquartile Range, DAS=Disease Activity Score, SLEDAI= Systemic Lupus Erythematosus Disease Activity Index

Table 5 represents the laboratory data of patients. The mean value of ESR was 39.8 ± 9.3, the mean value RF was 1.2 ± 0.4 (IU/mL**)**, the mean Hb was11.4 ± 1.6 (g/dl**)**, the mean WBCs was 6.1 ± 1.3 ($x10^3$/ul), the mean AST was 20.95 ± 8.2 (U/L), mean of ALT was 21.4 ± 9.1(U/L), the mean value of S. creatinine was 62.11 ± 14.3 mg/dl and mean of BUN was 5.83 ± 1.2.

Table (5): Laboratory Findings of Study group (A)

4		n = 80
ESR-1(mm/h)	**Mean ± SD**	39.84 ± 9.3
ESR-2(mm/h)	**Mean ± SD**	47.21 ± 11.2
RF Category (n=71) (IU/mL**)**	**Positive**	62 (87.3%)
	Negative	9 (12.7%)
Hb (g/dl)	**Mean ± SD**	11.37 ± 1.6
WBCs ($x10^3$/ul)	**Mean ± SD**	6.1 ± 1.3
Platelets ($x10^3$/ul)	**Mean ± SD**	260.56 ± 63.8
HbA1C (n=24) (%)	**< 6.4 mmol**	19 (79.2%)
	> 6.4 mmol	5 (20.8%)
AST (U/L)	**Mean ± SD**	20.95 ± 4.4
ALT(U/L)	**Mean ± SD**	21.42 ± 4.5
ALP(g/dl)	**Mean ± SD**	37.38 ± 9.2
Serum Creatinine (mg/dl)	**Mean ± SD**	62.11 ± 14.3
BUN (mg/dl)	**Mean ± SD**	5.83 ± 1.2
Urine Analysis	**Normal**	64 (80%)
	Abnormal	16 (20%)
Serum Uric Acid (mg/dl)	**Mean ± SD**	3.91 ± 0.9
Proteinuria (mg/L)	**Mean ± SD**	281.90 ± 76.9
Creatinine Clearance (ml/min)	**Mean ± SD**	76.40 ± 18.5
ANA (n=9) (ELISA**)** (IU/mL)	**Positive**	8 (87.3%)
	Negative	1 (12.7%)
Anti-Ds-DNA(n=9) (mg/dl)	**Positive**	6 (66.7%)
	Negative	3 (33.3%)
Cholesterol (mg/dl)	**High (> 200 mg/dl)**	12 (15%)
	Normal (< 200 mg/dl)	68 (85%)
Triglycerides (mg/dl)	**High (> 150 mg/dl)**	15 (18.7%)
	Normal (< 150 mg/dl)	65 (81.3%)
Low Density Lipoprotein (mg/dl)	**High (> 100 mg/dl)**	18 (22.5%)
	Normal (< 100 mg/dl)	62 (77.5%)
High Density Lipoprotein (mg/dl)	**Abnormal (< 60 mg/dl)**	10 (12.5%)
	Normal (> 60 mg/dl)	70 (87.5%)
AI (TG/HDL)	**High (>5)**	17 (21.2%)
	Normal (< 5)	63 (78.8%)

SD=Standard Deviation, IQR=Interquartile Range, ESR=Erythrocyte Sedimentation Rate, RF=Rheumatoid Factor, Hb=Hemoglobin, WBCs=White Blood Cells, HbA1C= hemoglobin A1c, AST=Aspartate Aminotransferase, ALT=Alanine Aminotransferase, ALP=Alkaline Phosphatase

DISCUSSION

Rheumatoid arthritis (RA), cutaneous lupus erythematosus, and systemic lupus erythematosus (SLE) are among the autoimmune illnesses that are commonly treated with hydroxychloroquine (HCQ). Both RA and SLE can be managed with the help of HCQ and its metabolites, which have been shown to have several positive effects on a variety of disease-related and comorbid outcomes, including lowering blood sugar, protecting against diabetes mellitus (DM), and enhancing lipid profile [(15)].

In early RA patients, **Schapink *et al.*** [(16)] evaluated the effectiveness of HCQ-Methotrexate (MTX) combined therapy with MTX alone and found that patients receiving HCQ in addition to regular MTX saw considerably improved short-term outcomes. The difference in the favorable EULAR response and the DAS28 score, however, were no longer statistically significant at the 12-month mark.

According to **Carmichael *et al.*** [(17)] findings from 2002, HCQ supports a higher exposure to MTX, which may account for the short-term improvement shown in the MTX-HCQ sample.

In present study, despite small sample size of SLE patients (11% of our patients) 33.3% of them with no flare, 55.6% with mild flare and only 11.1% with severe flare, which could be due to all of them were receiving HCQ.

The study on SLE patients receiving HCQ and showed HCQ beneficial effect on decreasing the risk of flares, diabetes mellitus [(18)], thrombotic events, and dyslipidemia. HCQ was reported to reduce damage accrual and improves the survival [(19)].

In our study, 30% of the patients had DM, 79.2% of those were controlled (HA1C less than 6.4 mmol) mostly due to long term HCQ use and its anti-hyper glycemic effect. The study found that HCQ reduced incidence of diabetes risk among RA patients [(20)]. An important American-wide observational cohort investigation by **Ozen *et al.*** [(21)] revealed that the prevalence of diabetes was greater in RA patients and that HCQ was linked to a decreased risk of diabetes among RA patients.

Findings by **Desai *et al.*** [(22)] showed that HCQ monotherapy decreased the risk of diabetes by 33%. The majority of prior studies support the positive changes in insulin sensitivity, release, and clearance that occur as a result of HCQ treatment and its positive effects on glucose metabolism.

According to **Baidya *et al.*** [(23)], the HbA1c level and insulin need were significantly reduced in the HCQ treated group in a dose-dependent manner.

Around 80% of the patients in the current study had normal levels of total cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), and atherogenic index (AI). This might be

accounted for by HCQ's influence on dyslipidemia. **Munro *et al.* [24]** provided evidence for this conclusion.

According to **Restrepo *et al.* [26]**, using HCQ was linked to lowering lipid levels in the RA group (LDL decreased by 9.3 mg/dL, TC decreased by 4.7 mg/dL, and AI increased by 0.59 [p0.001]).

CONCLUSION

It could be concluded that HCQ is associated with a reduced risk of rheumatic diseases and its associated comorbidities as SLE, thrombosis and diabetes.

RECOMMENDATIONS

Future studies using larger sample to confirm our result and more definitively explore the roles of therapy duration, race/ethnicity, and other factors, and measure blood level of HCQ.

LIMITATION

Our results had some limitations:

1- The sample size was relatively small which could affect the magnitude of association. It was a hospital-based study so selection bias cannot be excluded.
2- We did not measure blood level of HCQ so we cannot exclude patient nonadherence.
3- We did not evaluate blood glucose level and lipid profile before HCQ therapy and also not take into consideration other medication such as hypoglycemic and lipid lowering drugs, so could not distinguish improvement was due to HCQ therapy versus other medications.

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