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EVALUATION OF SAFETY AND EFFICACY OF HYDROXYCHLOROQUINE SULFATE AS AN ADJUNCT TO DIET AND EXERCISE TO IMPROVE GLYCEMIC CONTROL IN TYPE 2 DIABETES PATIENTS UNCONTROLLED ON SULFONYLUREAS + METFORMIN COMBINATION

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ABSTRACT

Purpose: To evaluate safety and efficacy of hydroxychloroquine (HCQ) in uncontrolled type 2 diabetes (T2D) patients receiving sulfonylureas+metformin combination. **Methods:** This prospective, multicentric, phase 4 study with 747 T2D patients uncontrolled (HbA1c≥7%) on sulfonylureas+metformin combination enrolled to receive add on HCQ 400 mg/day for 52 weeks. The modified intention to treat population comprised of 609 cases and 457 cases of per protocol population. Effects on glycemic, lipid and inflammatory parameters were assessed. **Results:** Significant fall in glycemic and lipid parameters were seen. Patients were divided based on their baseline hsCRP levels (≤3 and >3). There was significant fall in all parameters at week 24 & 52 irrespective of baseline hsCRP. However, fall in A1C was significantly more at week 12 and 24 in high inflammatory load ($p<0.0001$). Of the 191 adverse events in 111 patients most were GI related (26.2%), of mild intensity (85%) and 70% of which were unlikely related to HCQ. Total 9 serious adverse events were reported, 8 were unrelated and 1(anaemia) was probably or likely related to HCQ. **Conclusion:** T2D is characterized by chronic low grade inflammation. Hydroxychloroquine significantly reduced

glycemic parameters comparable to other oral hypoglycaemic agents with added benefits on lipid parameter. **Registration:** Clinical Trial Registry India (CTRI) (Registration Number: CTRI/2016/02/006599).

KEYWORDS: Glycemic control; Hydroxychloroquine; Metformin; Sulfonylureas; Type 2 Diabetes.

INTRODUCTION

Worldwide, the current diabetes burden has reached 540 million cases and estimated to cross 783 million by 2045. India contributed 774,194,700 cases of diabetes to global burden in 2021.[1] The complications associated with diabetes have resulted in increased morbidity and mortality,[2] and therefore it is necessary to control the progression of diabetes to reduce diabetes associated complications and deaths.

Improvement in glycemic profile in diabetes patients is also important for primary prevention of associated complications. Metformin is the drug of choice as a first-line treatment.[3] However, as the disease progresses, there is a need for additional anti-diabetic drugs to provide optimum glycemic control.[4] It has been hypothesized that combining metformin with other antidiabetic agents from another class may help to preserve β-cell function and thereby maintain a long-term glycemic efficacy or durability.[5] The safest choice of second line treatment, amongst available anti-diabetic drugs is sulfonylureas, which in combination with metformin, provide a sufficient glycemic control. However, sulfonylureas may lead to pancreatic exhaustion due to its long term use. In such cases, it is necessary to add a third line agent which can achieve the desired glycemic targets without compromising safety. Most of the available newer class of anti-diabetic drugs such as, gliptins, sodium glucose co-transporter 2 (SGLT2) inhibitors etc are either costly or are associated with safety concerns and therefore may not be preferred as third line agent if better choice is available.

Hydroxychloroquine (HCQ) is an oldest anti-malarial drug and its safety is well established through its use in chronic conditions like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). HCQ has also been evaluated for its anti-diabetic potential through multiple clinical studies. Animal studies as well as human pharmacodynamic studies have established its mechanism of action as a glucose lowering drug.[6-11]

Pilot study among non-diabetic obese subjects reported a significant increase in insulin sensitivity index (ISI) and trend towards reduced insulin resistance and insulin secretion after 6 weeks of HCQ therapy.[10] In another randomized double-blind trial in rheumatic patients by Wasko et al, HCQ improved ß cell function and insulin sensitivity in non-diabetic volunteers.[11] Besides this, an additional novel observation in this study was improvement in adiponectin levels, a mediator of favourable effects on glucose metabolism in HCQ treated group.

More recently, Rajput et al. reported that addition of HCQ as an add on drug in diabetes patients uncontrolled on glimepiride and metformin significantly improves beta cell function and Insulin resistance along with significant improvement in adiponectin, high sensitivity C-reactive protein (hsCRP) levels and Interleukin (IL-6) levels. The changes in homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta cell function (HOMA-B) correlated significantly with the changes in pro-inflammatory markers like IL-6, hsCRP and adiponectin and improvement in glycemic parameters like fasting plasma glucose (FPG), postprandial blood glucose (PPG) and glycated hemoglobin (HbA1c) at the end of 12 weeks therapy.[12]

Glycemic variability is a more meaningful measure of glycemic control. Recently, in another study, Rajput et al. evaluated glycemic variability parameters by continuous glucose monitoring after addition of HCQ 400 mg in diabetic patients uncontrolled on Glimepiride and Metformin. HCQ significantly reduced all parameters of glycemic variability like mean amplitude of glycemic excursion (MAGE), mean of daily differences (MODD), standard deviation of 24 hour blood glucose and average blood glucose at the end of 12 weeks therapy.[13]

In a prospective 6 months, randomized, double blind trial in treatment refractory diabetes patients, HCQ use was associated with average 30% reduction in insulin dose.[14] Pleiotropic benefits of HCQ include anti-hyperlipidemic, anti-platelet, anti-thrombotic, anti-inflammatory, and immunomodulatory effect.[15-26] A systematic review including three preclinical and fifteen clinical studies (55,776 study participants) showed significant improvement of lipid profile and insulin levels and substantial diminution of HbA1c, FPG, and PPG levels.[27]

In past, authors of this publication also conducted a double blind, double dummy, randomised, comparative, multicentric phase 3 study where anti-hyperglycaemic potential of HCQ was compared with pioglitazone in type 2 diabetes patients uncontrolled on metformin and sulfonylureas combination. The results of the study demonstrated comparable hypoglycaemic effects of HCQ to those of pioglitazone. Besides this, HCQ use was associated with beneficial effects on lipids.[28] Based on the results of this study, we received a marketing permission for HCQ 400 mg as an adjunct to metformin and sulfonylureas in type 2 diabetes patients.

As phase 4 studies are used to determine long term safety to identify adverse effects that may not have been reported during the phase 3 trials, we planned this prospective, open label, multicentric phase 4 study to generate additional data on long-term safety, tolerability and efficacy of HCQ 400 mg in wider type 2 diabetes population over a period of 52 weeks exposure to HCQ.

MATERIAL AND METHODS

This was a prospective, open label and multicentric phase 4 study conducted at 46 centres across India between June 2016 and December 2020. Type 2 diabetes patients uncontrolled on sulfonylureas and metformin combination for at least 3 months were screened for this study. The study was approved by ethics committee of each centre. Patient information sheet and informed consent form was provided in a language understood by the patient, and only those patients who gave their written consent to participate in the study prior to performing any study related procedure were screened. The execution and monitoring of the study was done in accordance with the ethical principles of Declaration of Helsinki and requirements of good clinical practice. The trial was registered on Clinical Trial Registry India (CTRI) (Registration Number: CTRI/2016/02/006599).

Male and female patients aged between 18 and 65 years, body weight > 60 kg, diagnosed with Type 2 Diabetes and uncontrolled on sulfonylureas and metformin combination were included. Patients receiving stable doses of sulfonylureas and at least 1000 mg metformin for at least 3 months with HbA1c ≥7% and ready to undergo a follow-up period of 52 weeks were screened for the study.

Patients diagnosed with diabetes other than type 2 diabetes, or already receiving or requiring insulin or with a history of any retinopathy of any grade including diabetic retinopathy, evidence of an imminent need for retinal laser therapy, uncorrected visual acuity <20/100, abnormal visual fields, difficulty to examine optic disc, or evidence of retinal pigment epithelial abnormalities and patients with history or risk of macular edema were excluded from the study. Patients with history of myalgia, aplastic anemia or agranulocytosis, granulocytopenia, psoriasis, porphyria, rash, scaling, scaling eczema, and glucose 6-phosphate deficiency (G6PD) or with significant cardiovascular, renal, hepatic, neurologic, hematologic illness limiting participation of patient in a clinical trial were also excluded. Patients with known history of HIV 1 or HIV 2, Hepatitis B or C viruses or syphilis infection or malignancy were excluded. Patients receiving hydroxychloroquine for any other illness like Rheumatoid Arthritis, Systemic Lupus Erythematosus etc. were not included in the study. Patients with a history of hypersensitivity to the study drug formulations or substance abuse or participation in a clinical trial within the last 30 days prior enrollment were excluded from the study. Also, Pregnant or lactating women or women of childbearing potential not practicing contraception were excluded.

Subjects consented to participate in the study were screened for their medical history, previous and current medication(s), details of diabetes history (duration of diabetes and duration and dose of anti-diabetic treatment), complete physical examination and vital signs etc. Blood samples were obtained to perform tests for HbA1c, Fasting Blood Glucose (FBG), 2-hr PPG, routine haematology, hs-CRP and creatine phosphokinase [CPK] lipid profile (Total Cholesterol [TC], triglycerides [TG], High Density Lipoprotein [HDL], non-High Density Lipoprotein [non-HDL] and Low density Lipoprotein [LDL]). Electrocardiogram (ECG), routine urinalysis and a test to assess G6PD was also done. Additionally, detailed ophthalmology examination (visual acuity test, fundoscopic test, visual field test, expert slit lamp test and amsler grid test) was also performed at screening visit. Urine pregnancy test was also performed to rule out pregnancy.

Patients who fulfilled all the eligibility criteria additionally received HCQ 400 mg orally once daily for 52 weeks and were asked to visit respective study sites for follow-up visits at week 4, week 8, week 12, week 24, week 36 and end of study visit at week 52. At each of the follow-up visits, physical examinations, vital signs, safety assessments, and hypoglycemia assessment were performed. Blood samples were also collected to perform FBG and 2-hr

PPG at each visit. Test for HbA1c was also performed at week 12, week 24 and week 52. Additionally, at week 52, haematology, biochemistry, lipid profile, ECG and routine urinalysis were also performed. At end of the study visit (week 52), all the laboratory investigations along with physical examination, ophthalmology examination and safety assessments were performed. Patients experiencing any Adverse Events (AE) or Serious Adverse Events (SAEs) were attended accordingly and treated as per principal investigator's discretion. The same information was duly recorded in respective Case Report Forms (CRFs).

Formal sample size calculations were not performed for this study. The sample size determination of 500 subjects was based on Drugs Controller General of India (DCGI) recommendation for conducting a phase 4 study to assess the long-term safety and efficacy of hydroxychloroquine.

Descriptive statistics were used to represent the demographic and baseline disease characteristics. Data are presented in terms of mean ± SD, median, percentiles or range for continuous variables and n (%) for categorical variables. Mean change in HbA1c, FBG and 2-hr PPG from baseline to Week 24 and Week 52 (end of therapy) were assessed by paired t-test. Mean change in lipid profile (total cholesterol, triglycerides, HDL and LDL) from baseline to Week 24 and Week 52 was assessed by paired t-test. Adverse events (clinical and laboratory) and incidence of hypoglycemia were represented as n (%). Changes in laboratory parameters at Week 24 and Week 52 were assessed by paired t-test. The per-protocol population was divided into two groups according to their hsCRP values at baseline (hsCRP ≤ 3 and > 3). These two sub-groups were compared for change in glycemic parameters (HbA1c, FBG and PPG) at week 12, 24 and 52 using two sample t-test for between group comparison and paired t-test for within group comparison. Change in lipid parameters (LDL, TC, Non-HDL, HDL and TG) and inflammatory parameters (HsCRP, WBC and ESR) at week 24 and week 52 were also assessed between the subgroups using two sample t-test for between group comparison and paired t-test for within group comparison. Level of significance was set at 0.05 and statistical analysis was performed using SAS 9.3.

RESULTS

A total of 1719 patients were screened between 23rd June, 2016 and 23rd October, 2019, of which 747 patients who satisfied study eligibility criteria were enrolled in the study and 457 patients completed the study till week 52 as per protocol. There were 31 cases of protocol violation and 259 patients were discontinued or withdrawn due to various reasons; lost to

follow-up (n=127), withdrawn consent (n=52), and insufficient therapeutic response (n= 52) were the 3 most common reasons **(Figure 1).**

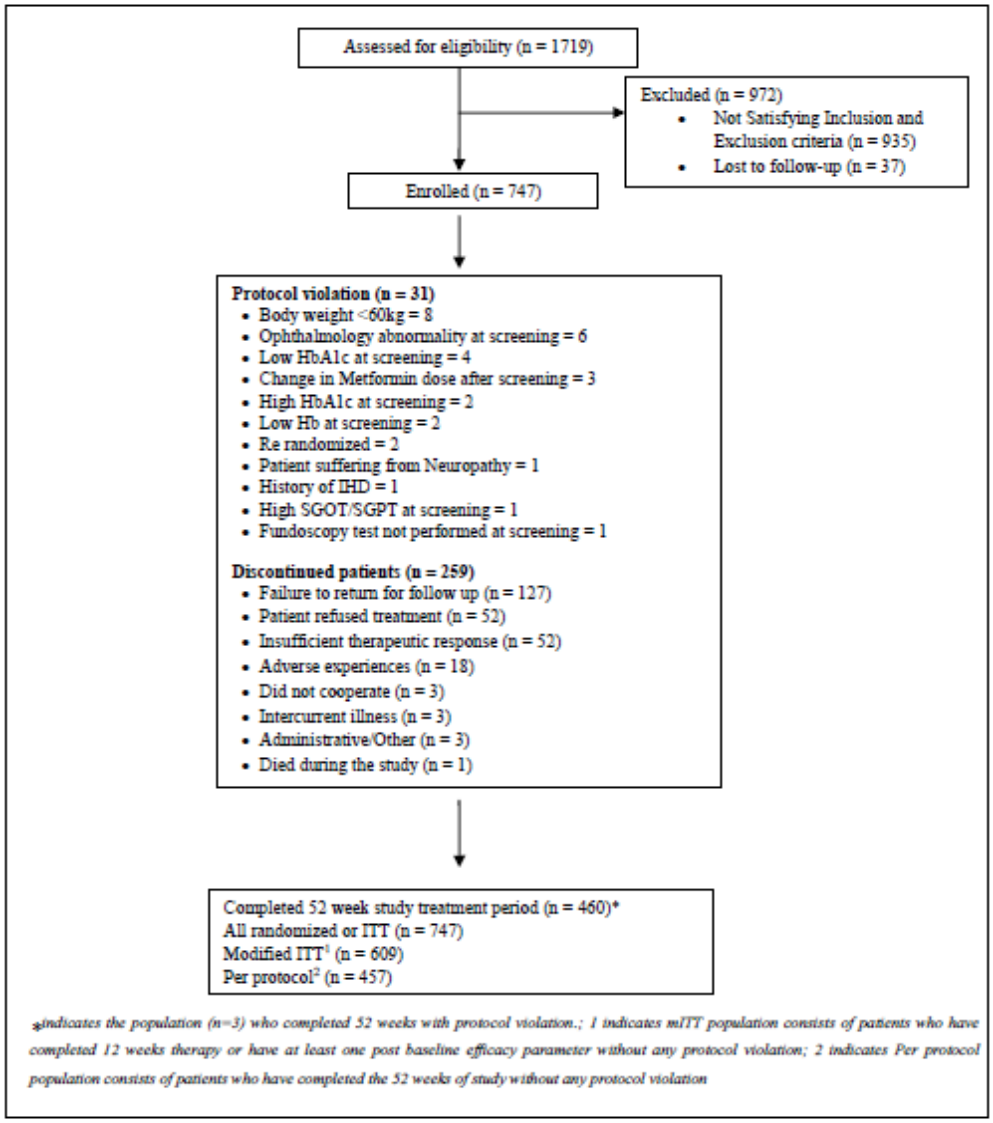

Fig. 1: Flow diagram for disposition of study participants.

Demographics

Of the 747 enrolled patients, 393 (52.61%) were females and average age of the population was 49.29 years. Duration of diabetes was 4.67 years and average HbA1c was 8.99 %. Majority of patients (87%) were receiving glimepiride-metformin combination as their prior anti-diabetic therapy. The detailed demography and baseline characteristics are presented in **Table 1.**

Table 1: Demography and Baseline disease characteristics of enrolled patients.

Parameters	Total (n= 747)
Sex[a]	
Female	393 (52.61)
Male	354 (47.39)
Age (years)[b]	49.29 ± 8.33
Weight (kg)[b]	71.02 ± 8.75
BMI (kg/m^2)	27.36 ± 3.79
Duration of diabetes (Years)[b]	4.67 ± 3.79
HbA1c (%)[b]	8.99 ± 1.21
FBG (mg/dL)[b]	160.33 ± 42.53
PPG (mg/dL)[b]	256.88 ± 66.65
TG (mg/dL)[b]	164.35 ± 82.53
TC (mg/dL)[b]	181.27 ± 44.15
LDL (mg/dL)[b]	107 ± 37.48
HDL (mg/dL)[b]	43.18 ± 12.99
Non-HDL (mg/dL)[b]	138.1 ± 42.93
Sulfonylurea consumption[a]	
Glimepiride	650 (87.01)
Gliclazide	97 (12.99)
Doses of prior anti-diabetic medication[a]	
Glimepiride 4 mg	603 (80.72)
Gliclazide 160 mg	47 (6.29)
Metformin 1000 mg	486 (65.06)

a-Values presented as n (%); b-Value presented as mean ± SD

Safety

List of adverse events reported during the study are summarized in **Table 2**. Overall, treatment with HCQ was safe and well tolerated. A total of 111 patients reported 191 adverse events during the study period. Almost 85% of the AEs were mild in intensity and 70% of the AEs were unlikely related to the study drug in investigator's opinion. Most frequently reported non-serious AEs were GI side effects (n= 50; 26.18%). Hypoglycemia was reported by 13 patients and there were total 22 hypoglycemia events. No patient reported severe hypoglycemia during the study. Non-proliferative diabetic retinopathy (NPDR) was observed in 11 patients, all were mild in intensity except 1. In the investigator's opinion, 9 events of NPDR were unlikely related to HCQ, 1 was possibly related and 1 was probably or likely related to HCQ. Nine serious adverse events were reported during the study where majority of the incidents were unlikely except anaemia which was a probable or likely adverse event of hydroxychloroquine. All the patients who reported the SAEs were either discontinued from the study or given symptomatic treatment depending on the opinion of the concerned

physician and were recovered except one death from lung carcinoma which was unrelated to the treatment in the investigator's opinion.

Table 2: Non serious adverse events reported during the study.

Adverse Events	Hydroxychloroquine (n= 747) n (%)
Gastrointestinal disorders	50 (26.18)
Metabolism and nutrition disorders	29 (15.18)
Eye Disorders	24 (12.57)
Nervous system disorders	22 (11.52)
Skin and subcutaneous tissue disorders	15 (7.85)
General disorders and administration site conditions	12 (6.28)
Infections and infestations	11 (5.76)
Musculoskeletal and connective tissue disorders	9 (4.71)
Respiratory, thoracic and mediastinal disorders	8 (4.19)
Investigations	6 (3.14)
Cardiac disorders	1 (0.52)
Infections and infestations/General disorders and administration site conditions	1 (0.52)
Injury, poisoning and procedural complications	1 (0.52)
Psychiatric disorders	1 (0.52)
Renal and urinary disorders	1 (0.52)
Total	191

Efficacy

Out of the 747 enrolled patients, 609 patients, who completed at least 12 weeks of therapy and reported at least 1 post baseline efficacy observation, without any protocol violation were termed as mITT population and 457 patients who completed the study for total 52 weeks without any protocol violation were termed as per protocol population. Both the study groups were evaluated for efficacy parameters.

The mean HbA1c at baseline was 8.91%. At Week 12, Week 24, and Week 52 there was a significant reduction in HbA1c from baseline ($p<0.0001$). The mean HbA1c at Week 52 was 8.1%. Table 3 shows a change in HbA1c at Week 12, 24 and 52 from baseline. At Week 52, 24% of patients achieved HbA1c<7% and 38% of patients achieved HbA1c < 7.5%. **(Table 3)**

Table 3: Changes in HbA1c.

Parameters HbA1c (%)	mITT population[b] (n= 609)	PP population[c] (n = 457)		
		hsCRP ≤ 3 (n = 255)	hsCRP> 3 (n = 202)	P value[d]
Baseline[a]	8.91 ± 1.17	8.81 ± 1.14	8.95 ± 1.18	0.1855
Change at Week 12[a]	-1.18 ± 1.28	-1.24 ± 1.21	-1.53 ± 1.15	0.0102
P value*	<0.0001	<0.0001	<0.0001	
Change at Week 24[a]	-1.17 ± 1.43	-1.31 ± 1.26	-1.53 ± 1.2	0.0505
P value*	<0.0001	<0.0001	<0.0001	
Change at Week 52[a]	-0.80 ± 1.53	-0.90 ± 1.52	-0.96 ± 1.39	0.6752
P value*	<0.0001	<0.0001	<0.0001	

** indicates p value and paired t-test used for the comparison with baseline readings;*

aIndicates mean ± SD

bModified intention-to-treat (mITT) population comprise of patients who have completed week 12 or have at least one post baseline efficacy parameter without any protocol violation

cPer protocol (PP) population comprise of patients who have completed the 52 weeks of study without any protocol violation.

dIndicates p value and two sample t-test used for the comparison

Changes in lipid profile (TC, TG, LDL-C, HDL-C, and non-HDL-C) were assessed at Week 24 and Week 52 from baseline. With the use of hydroxychloroquine, there was significant reduction ($p<0.05$) in total cholesterol, LDL-C, and non-HDL-C. There was an absolute reduction of 5.92%, 9.19 % and 8.06% at Week 52 in TC, LDL-C and non HDL-C respectively. Although not significant, but there was a fall in TG levels at week 52 from baseline and an increase in HDL at week 52 from baseline. Refer **Table 4** for changes in lipid parameters.

Diabetes is also termed as meta-inflammatory disorder. hsCRP being an inflammatory marker was assessed in this study. The per-protocol population was divided into two groups according to their hsCRP values at baseline (hsCRP ≤ 3 and > 3). Of the 52% females enrolled, >60 % had high inflammatory load at baseline. There was significant fall in A1c, FBG, PPG, LDL-C, TG, TC, HDL & non-HDL-C at week 24 & 52 irrespective of baseline hsCRP. However, fall in A1C was significantly more at week 12 and 24 in high inflammatory load (hsCRP>3) patients along with significant fall in hsCRP at week 24 and 52 from baseline ($p<0.0001$) **(Table 4).**

There was a significant reduction in mean FBG and PPG from baseline at all visits throughout the study ($p<0.05$). Overall, there was a fall of 6.63 mg/dL in FBG and a fall of 27.8 mg/dL in PPG at week 52 from baseline. **(Table 4)**

Table 4: Changes in Glycemic, Lipid Parameters and Hs-CRP.

Parameters	mITT population[b] (n= 609)	PP population[c] (n = 457)	
		hsCRP ≤ 3 (n = 255)	hsCRP> 3 (n = 202)
FBG (mg/dL)			
Baseline[a]	159.61 ± 41.62	155.11 ± 39.72	159.96 ± 43.66
Change at Week 12[a]	-21.47 ± 49.01*	-22 ± 44.98*	-30.21 ± 45.73*
Change at Week 24[a]	-15.33 ± 53.91*	-18.52 ± 49.63*	-26.56 ± 45.81*
Change at Week 52[a]	-6.63 ± 61.05*	-12.37 ± 54.93*	-8.65 ± 59.52*
PPG (mg/dL)			
Baseline[a]	257.57 ± 65.9	258.29 ± 67.95	250.57 ± 64.26
Change at Week 12[a]	-47.74 ± 80.6*	-60.8 ± 78.94*	-50.68 ± 76.92*
Change at Week 24[a]	-38.79 ± 93.42*	-48.49 ± 92.73*	-46.34 ± 79.45*
Change at Week 52[a]	-27.8 ± 96.86*	-41.13 ± 92.42*	-24.01 ± 97.73*
TC (mg/dL)			
Baseline[a]	181.07 ± 43.69	175.56 ± 42.72	179.43 ± 43.85
Change at Week 24[a]	-11.74 ± 36.94*	-13.43 ± 38.16*	-13.13 ± 38.45*
Change at Week 52[a]	-10.72 ± 39.24*	-10.88 ± 40.16*	-11.59 ± 40.09*
LDL (mg/dL)			
Baseline[a]	106.44 ± 37.36	101.72 ± 35.63	105.69 ± 37.45
Change at Week 24[a]	-10.52 ± 30.69*	-11.21 ± 30.72*	-11.92 ± 31.59*
Change at Week 52[a]	-9.79 ± 33.5*	-9.29 ± 33.72*	-10.84 ± 34.01*
Non-HDL (mg/dL)			
Baseline[a]	137.86 ± 42.39	131.52 ± 41.72	136.19 ± 42.85
Change at Week 24[a]	-12.36 ± 37.88*	-13.59 ± 39.3*	-13.79 ± 39.11*
Change at Week 52[a]	-11.12 ± 39.46*	-10.96 ± 42.09*	-12.26 ± 40.92*
TG (mg/dL)			
Baseline[a]	164.71 ± 81.5	158.0 ± 83.00	161.69 ± 79.95
Change at Week 24[a]	-7.02 ± 99.2	-12.67 ± 76.88	-11.59 ± 83.95
Change at Week 52[a]	-4.18 ± 100.13	-7.26 ± 94.04	-8.58 ± 83.41*
HDL (mg/dL)			
Baseline[a]	43.21 ± 12.67	44.04 ± 13.63	43.23 ± 13.27
Change at Week 24[a]	0.62 ± 14.12	0.16 ± 15.44	0.66 ± 14.39
Change at Week 52[a]	0.39 ± 14.16	0.08 ± 16.83	0.67 ± 15.58
Hs-CRP (mg/dL)			
Baseline[a]	4.25 ± 4.79	1.42 ± 0.78	7.78 ± 5.44
Change at Week 24[a]	-0.34 ± 5.43	0.69 ± 3.95*	-2.04 ± 6.72*
Change at Week 52[a]	0.2 ± 7.63	0.70 ± 3.13*	-1.23± 8.90*
WBC (/cu mm)			
Baseline[a]	8120.9 ± 1915.92	7485.71 ± 1585.19	8723.76 ±1882.01
Change at Week 24[a]	-246.97 ± 1778.66	-139.72 ± 1718.25	-311.93 ± 1760.85
Change at Week 52[a]	7927.91 ± 2005.84	-140.28 ± 1847.43	-308.12 ± 2008.11

ESR (mm/h)			
Baseline[a]	19.34 ± 14.41	15.22 ± 11.82	24.05 ± 16.94
Change at Week 24[a]	17.4 ± 12.93	-1.58 ± 10.55	-1.88 ± 13.50
Change at Week 52[a]	-2.47 ± 12.35	-0.83 ± 11.68	-4.40 ± 14.40

**Indicates p<0.0001 and paired t-test used for the comparison with baseline values*

aIndicates mean ± SD

bModified intention-to-treat (mITT) population comprise of patients who have completed week 12 or have at least one post baseline efficacy parameter without any protocol violation

cPer protocol (PP) population comprise of patients who have completed the 52 weeks of study without any protocol violation

DISCUSSION

Diabetes is an inflammatory condition and if left uncontrolled, it can lead to several complications. Insulin resistance and type 2 diabetes are associated with an array of plasma lipid and lipoprotein anomalies including decreased HDL, LDL cholesterol and increased triglyceride levels. [29] So, diabetes patients require multiple drugs to keep their sugar in control. Even after using two to three hypoglycaemic combinations, patients are still facing issues either with the uncontrollable sugar levels or with the long term adverse effects of the drugs. Hydroxychloroquine has a well established safety profile and its multifaceted effects on blood glucose and lipid lowering activity has also been well-documented in previously published literatures.[30]

Previously we evaluated the comparative safety and efficacy of HCQ against pioglitazone in type 2 DM patients uncontrolled on sulfonylureas + metformin combination. HCQ demonstrated comparable safety and efficacy in this study with additional lipid lowering benefits (significant fall in TC, LDL and non HDL-C). [28] To further validate the findings of this study in wider population, we conducted this large-scale, multi-centric Phase 4 study to assess efficacy, tolerability and to identify adverse events of hydroxychloroquine 400 mg in larger T2D population uncontrolled on metformin and sulfonylureas combination.

Safety of HCQ is well established through its use in various chronic illnesses like RA and SLE. Similarly, HCQ was well tolerated in our study; most commonly reported non-serious AEs were GI related which is known with use of HCQ. [31] Adverse events reported during our study were similar to those of previously known with the drug. Similarly, hypoglycemia, as reported previously, was reported by 2% of the patients in this study (13 patients reported

22 events of hypoglycaemia). Adverse events reported in this study were of mild to moderate in nature that didn't require any external assistance.

Retinal toxicity from Chloroquine and its analogue HCQ has been recognized for many years. Chloroquine toxicity remains a problem in many parts of the world, but is seen less frequently in the United States where the drug largely has been replaced by HCQ. [32] Although, retinal toxicity is not rare among long-term users of HCQ, it is highly dependent on the daily dose by weight. [33] It also has been found that the classic "bull's-eye" distribution of toxicity is infrequent in patients of Asian heritage who typically show early damage in a more peripheral pattern. Retinopathy is also one of the complications of diabetes itself where HCQ is indicated. Thus proper ophthalmology screening is essential before initiating study with HCQ. It is important to note that goal of screening for retinopathy is not to stop valuable drugs at the first borderline abnormality, but to recognize definite signs of toxicity at a primitive stage to avert visual acuity loss. So, we performed detailed ophthalmology examination at screening (to rule out any ophthalmology abnormality), week 12 and week 52 (to see if there are any ophthalmology abnormalities during use of HCQ).

In our Phase 4 study, NPDR (Non-Proliferative Diabetic Retinopathy) was reported in 1.47% patients (11 out of 747 patients eligible for safety evaluation). As per study protocol, the study treatment was discontinued after NPDR reporting in these cases. All the events reported were of mild intensity except for 1 female patient for whom investigator reported severe NPDR. In the opinion of the study investigator, the causality for majority (9 out of 11 patients, 81%) of events was reported as 'Unlikely' related to HCQ treatment, one event was 'Possibly' related and one event was 'Probable/likely' related to the study treatment. There was no event that was certainly related to HCQ treatment in the opinion of investigator. Since this was a Phase 4 trial, there was no control group to compare the incidence of NPDR with HCQ treatment. However, in a comparative Phase 3 study that was conducted by Ipca, the incidence of NPDR in Pioglitazone comparator group was 1.51% (2 out of 132 patients) as compared to 0.74% in hydroxychloroquine group (1 out of 135 patients). The study population was similar in both Phase 3 and Phase 4 study (i.e., T2D patients uncontrolled on metformin and sulfonylureas).[28] These incidence rates of HCQ treatment associated NPDR doesn't appear higher than the incidence of NPDR from other antidiabetic drugs.[34]

Recently in Taiwan, 12 year data from National Health Insurance Research database of 47,353 newly diagnosed T2D patients was retrospectively evaluated to study the relationship

between HCQ and diabetic retinopathy by Chen HC et al., 2021 using multivariate analysis model. They observed that, the use of HCQ in patients of rheumatoid diseases with T2D did not show any significant increase in risk of diabetic retinopathy (OR 1.07, 95% CI, 0.80-1.42).[35]

A cohort study by Melles et al. reported cumulative incidence of retinopathy as 2.7% after 15 years of HCQ administration in patients with co-morbid T2D, where majority of cases were mild and incidence of moderate to severe retinopathy was just 1.1%.[36] However, the authors didn't find any association between diabetes and the risk of HCQ retinopathy.[37] A number of literatures have been published showing the prevalence of NPDR upto 45% in Indian population which is much higher than the prevalence of Asian population which explains the incidence of NPDR in our study.[38]

In a retrospective analysis of medical records of Indian RA patients who also had T2D, Baidya A., 2021 evaluated the effects of HCQ on the progression of diabetic retinopathy (DR). The patients studied in this evaluation received Metformin and Sulfonylureas in addition to either HCQ or Pioglitazone. He observed that, the progression from mild to moderate NPDR over 3.5 years occurred in 2 out of 18 (11%) eyes in HCQ group and 8 out of 14 (57%) eyes in the Pioglitazone group respectively, representing a significant relative risk reduction with HCQ treatment ($p<0.001$). No patients had progressed from mild NPDR to severe NPDR in the HCQ group, whereas 2 eyes had progressed from mild to severe NPDR in the Pioglitazone group.[39] This indicates that, progression of DR from mild to moderate NPDR or severe NPDR may be delayed by HCQ treatment. Despite several decades of use of HCQ in RA and lupus with co-morbid T2D, excess risk of NPDR is not reported and no specific box warning or precaution has been mentioned for diabetic retinopathy complications. Rather, risk factors like poor glycemic control, age, duration of diabetes, number of anti-diabetic medications, hypertension and hyper-lipidemia has been found as possible reason behind the causation of NPDR in our study. Hence, the cases of NPDR reported in this phase 4 study might be an outcome of DM progression rather than hydroxychloroquine use.

Besides these non-serious AEs, Nine SAEs were reported during our study, 8 were unlikely or not related to the study drug in investigator's opinion. The SAE of anemia was likely related to the study drugs in the opinion of investigator. Overall treatment with HCQ was safe and well tolerated.

The patient population enrolled in this study had a mean baseline HbA1c of 8.91% indicating severity of the disease. Addition of HCQ to existing antidiabetic regimen in study population showed a significant reduction in HbA1c, FBG, and PPG throughout the study till week 52. In our study, there was a fall of 1.18%, 1.17% and 0.8% in HbA1c at week 12, week 24, and week 52 respectively from baseline. The fall in HbA1c observed in our study was similar to the fall observed with other oral hypoglycaemic agents.[40] Typically, a fall of 0.3 to 0.4 % in HbA1c is considered significant to estimate the magnitude of treatment effect.[41] Significant reduction was also observed in total cholesterol and LDL-C levels from baseline at week 24 and 52. This reduction was similar to that obtained in previously conducted Phase 3 study on HCQ.[28]

Diabetes has also been linked with elevated systemic inflammatory markers. So, we evaluated hsCRP, WBC, and ESR in our study. Patients were divided based on their baseline hsCRP levels in subgroups of hsCRP ≤3 and hsCRP >3. Of the 52% females enrolled >60 % had high inflammatory load at baseline. The fall in HbA1c in patients with hsCRP>3 is significantly higher than those with baseline hsCRP≤3. Similar association was also reported by Baidya et al. in their multicentric, open labeled comparative observational study. They found that hsCRP levels correlated with HbA1C levels. Patients who are having high hsCRP i.e., ≥ 3 had higher impact in HbA1c after prolong use of HCQ. Even Patients with moderately elevated hsCRP (≥ 2) had an impact on HbA1c. The authors further found that by reducing hs-CRP by ≥1 was correlating with reduction of HbA1c in a range of 0.8-1.3%.[42] This indicates that patients with high inflammatory load are likely to benefit more with HCQ treatment.

CONCLUSION

Our study highlighted that hydroxychloroquine is well-tolerated, safe and effective as an anti-diabetic agent in T2D patients inadequately controlled on a combination of metformin and sulfonylureas. Besides this, beneficial effects on lipids as observed in our study and other multifaceted effects like cardio-protective, anti-platelet, and anti-thrombotic effects could make hydroxychloroquine a preferred anti-diabetic agent.

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REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, Brussels, Belgium: International Diabetes Federation, 2021; 10.
2. Naslafkih A, Sestier F. Diabetes mellitus related morbidity, risk of hospitalization and disability. J Insur Med, 2003; 35(2): 102–13.
3. Holman R. Metformin as first choice in oral diabetes treatment: the UKPDS experience. Journ Annu Diabetol Hotel Dieu, 2007; 13–20.
4. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes. Agency for Healthcare Research and Quality. Rockville MD: US, 2007.
5. Zinman B. Initial combination therapy for type 2 diabetes mellitus: Is it ready for prime time? Am J Med, 2011; 124 (1): 19–34.
6. Emami J, Gerstein HC, Pasutto FM, Jamali F. Insulin-sparing effect of hydroxychloroquine in diabetic rats is concentration dependent. Can J Physiol Pharmacol, 1999; 77(2): 118–23.
7. Emami J, Pasutto FM, Mercer JR, Jamali F. Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. Life Sci, 1999; 64(5): 325–35.
8. Abdel-Hamid AAM, El-Firgany AE-DL. Hydroxychloroquine hindering of diabetic isletopathy carries its signature on the inflammatory cytokines. J Mol Histol, 2016; 47(2): 183–93.
9. Abdel-Hamid AAM, Firgany AE-DL. Favorable outcomes of hydroxychloroquine in insulin resistance may be accomplished by adjustment of the endothelial dysfunction as well as the skewed balance of adipokines. Acta Histochem, 2016; 118(6): 560–73.
10. Mercer E, Rekedal L, Garg R, Lu B, Massarotti EM, Solomon DH. Hydroxychloroquine improves insulin sensitivity in obese non-diabetic individuals. Arthritis Res Ther, 2012; 14(3):135.

11. Wasko MCM, McClure CK, Kelsey SF, Huber K, Orchard T, Toledo FGS. Antidiabetogenic effects of hydroxychloroquine on insulin sensitivity and beta cell function: a randomised trial. Diabetologia, 2015; 58(10): 2336–43.
12. Rajput R, Upadhyay P, Rajput S, Saini S, Kharab S. Effect of hydroxychloroquine on beta cell function, insulin resistance, and inflammatory markers in type 2 diabetes patients uncontrolled on glimepiride and metformin therapy. Int J Diabetes Dev Ctries, 2023.
13. Rajput R, Saini S, Rajput S, Upadhyay P. Effect of hydroxychloroquine on glycemic variability in type 2 diabetes patients uncontrolled on glimepiride and metformin therapy. Indian J Endocrinol Metab, 2022; 26(6): 537.
14. Quatraro A, Consoli G, Magno M. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus: A new job for an old drug? Annals of Internal Medicine, 1990; 112: 678–81.
15. Olsen NJ, Schleich MA, Karp DR. Multifaceted effects of hydroxychloroquine in human disease. Semin Arthritis Rheum, 2013; 43(2): 264–72.
16. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. Am J Med, 1994; 96: 254–9.
17. Morris SJ, Wasko MCM, Antohe JL, Sartorius JA, Kirchner HL, Dancea S, et al. Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. Arthritis Care Res (Hoboken), 2011; 63(4): 530–4.
18. Rahman P, Gladman DD, Urowitz MB, Yuen K, Hallett D, Bruce IN. The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. J Rheumatol, 1999; 26(2): 325–30.
19. Johnson R, Green JR, Charnley J. Pulmonary embolism and its prophylaxis following the Charnley total hip replacement. Clin Orthop Relat Res, 1977; 127: 123-32.
20. Johnson R, Gharnley J. Hydroxychloroquine in prophylaxis of pulmonary embolism following hip arthroplasty. Clin Orthop Relat Res, 1979; 144: 174-7.
21. Loudon JR. Hydroxychloroquine and postoperative thromboembolism after total hip replacement. Am J Med, 1988; 85(4): 57–61.
22. Achuthan S, Ahluwalia J, Shafiq N, Bhalla A, Pareek A, Chandurkar N. Hydroxychloroquine's efficacy as an anti-platelet agent study in healthy volunteers - a proof of concept study. J Cardiovasc Pharmacol Ther, 2015; 20(2): 174–80.

23. Pons-Estel GJ, Alarcón GS, Mcgwin G. Protective Effect of Hydroxychloroquine on Renal Damage in Patients with Lupus Nephritis: Data from LUMINA, a Multiethnic U. S Cohort Arthritis Rheum Jun, 2009; 61: 830–9.
24. Alarcon GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alen J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis, 2007; 66(9): 1168–72.
25. Hahn BH, Mcmahon M, Wilkinson A. American College of Rheumatology Guidelines for Screening, Case Definition, Treatment and Management of Lupus Nephritis. Arthritis Care Res (Hoboken), 2012; 64: 797–808.
26. Li X, Wang Y, Agostinis P, Rabson A, Melino G, Carafoli E, et al. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis, 2020; 11(7).
27. Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. Potential effect of hydroxychloroquine in diabetes mellitus: A systematic review on preclinical and clinical trial studies. J Diabetes Res, 2020: 1–10.
28. Pareek A, Chandurkar N, Thomas N, Viswanathan V, Deshpande A, Gupta OP, et al. Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with pioglitazone. Curr Med Res Opin, 2014; 30(7): 1257–66.
29. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care, 2004; 27(6): 1496–504
30. Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Ther Adv Endocrinol Metab, 2014; 5(4): 77–85.
31. Plaquenil® Hydroxychloroquine sulphate Prescribing Information [Internet]. Accessdata.fda.gov. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/009768s053lbl.pdf.
32. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol, 2014; 132(12): 1453.
33. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology, 2016; 123(6): 1386–94.
34. Kawasaki R, Kitano S, Sato Y, Yamashita H, Nishimura R, et al. Factors associated with non-proliferative diabetic retinopathy in patients with type 1 and type 2 diabetes: the

Japan Diabetes Complication and its Prevention prospective study (JDCP study 4). Diabetol Int, 2019; 10(1): 3–11.

35. Chen H-C, Lin H-Y, Chou MC-Y, Wang Y-H, Leong P-Y, Wei JC-C. Relationship of hydroxychloroquine and ophthalmic complications in patients with type 2 diabetes in Taiwan. Int J Environ Res Public Health, 2021; 18(15): 8154.
36. Melles RB, Jorge AM, Marmor MF, Zhou B, Conell C, Niu J, et al. Hydroxychloroquine dose and risk for incident retinopathy: A cohort study. Ann Intern Med, 2023; 176(2): 166–73.
37. Pareek A, Chandurkar N, Naidu K.Hydroxychloroquine Retinopathy- Safe dose at sight finally. Am. Coll. Physicians Obs, 2023.
38. Yang QH, Zhang Y, Zhang XM, Li XR. Prevalence of diabetic retinopathy, proliferative diabetic retinopathy and non-proliferative diabetic retinopathy in Asian T2DM patients: a systematic review and Meta-analysis. Int J Ophthalmol, 2019; 12(2).
39. Baidya A. Effects of hydroxychloroquine on progression of Diabetic Retinopathy in subjects with Rheumatoid Arthritis and Type 2 Diabetes Mellitus. Curr Diabetes Rev, 2022; 18(9).
40. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels. Diabetes Care, 2010; 33(8): 1859–64.
41. Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. CDER, 2008.
42. Baidya A, Chakravarti HN, Saraogi RK, Gupta A, Ahmed R, Banerjee A, et al. Efficacy of maximum and optimum doses of hydroxychloroquine added to patients with poorly controlled type 2 diabetes on stable insulin therapy along with glimepiride and metformin: Association of high-sensitive C-reactive protein (Hs-CRP) and glycosylated haemoglobin (Hba1c). Endocrinol Metab Syndr, 2018; 07(01).