METAbolic Effects of HydroxyChloroQuine

META-HCQ

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History of Significant Protocol Changes

Summary Significant Changes Version 1.4 3/MAY/2012

Change of inclusion criteria #1

Increased inclusion upper age limit to 75

Summary Significant Changes Version 1.3 13/MAR/2012

Addition of name of sub-investigator

Scott Goodwin, MD
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Removal of Oral Glucose Tolerance Testing (OGTT) as secondary endpoint of study:

Deleted page 6: "..2-hour glucose after ingestion of 75 grams of glucose in a standard OGTT, AUC of the glucose values during the OGTT, and"

Justification: Removal of the OGTT as secondary endpoint due to redundancy with the hyperinsulinemic euglycemic clamp.

Deleted all instances of OGTT as a procedure for this study: Pages, 6, 7, 8, 9, and 10

Edited Table of Study Procedures:

Deleted 2 visits and OGTT

Edited Clamp procedure to correct time required:

Page 8: deleted "90 min" replaced with "beginning of a **150** minute baseline …" and deleted "26" and replaced with "… out at 40 mU/m^2/min in an…"

Page 9: deleted "6 to 7" replaced "This visit takes **8-9** hours. "

Deleted type of future lab test:

Page 9: deleted "…including crp, IL6 and others."

Revised subject compensation: Now $25 for screen visit and $175 for each clamp visit – Total $375

Summary of Significant Changes Version 1.2 08/DEC/11

Addition of names of non-engaged study staff:

Anne Carol Goldberg, MD
Associate Professor of Medicine
Carlos Bernal-Mizrachi, MD
Assistant Professor of Medicine

Deleted sentence page 11, paragraph 1: Safety Reports will be generated ad hoc and reported as per HRPO policy and at least annually at the time of HRPO renewal.

Replaced with sentence page 11, paragraph 1: Safety Reports will be generated after 50% of patients have completed the study for review by the non-engaged study safety monitors, and reported as per HRPO policy and at least annually at the time of HRPO renewal.

Metabolic Effects of HYDROXYCLOROQUINE: Meta-HCQ

INTRODUCTION, BACKGROUND AND SIGNIFICANCE

Atherosclerosis, manifested as coronary artery disease, cerebrovascular disease and peripheral vascular disease, remains the number one cause of mortality in the United States. Advances in the management of risk factors and in the acute treatment of vascular events has reduced cardiovascular disease (CVD) mortality, but ongoing "westernization" of lifestyles has produced increasing numbers of persons at risk, and consequently an ever increasing public health burden. Persons with the metabolic syndrome, pre-diabetes or diabetes are known to have an increased risk of CVD and higher mortality from vascular events.[1] This increased risk has continued despite improved treatments and lower targets for hyperglycemia, blood pressure and hyperlipidemia.[2] The persistence of CVD as a major cause of morbidity and mortality underscores the need to understand the molecular mechanisms involved in atherosclerosis development and progression. The ultimate goal is to design safe and effective therapy that can mitigate the residual risk of CVD, especially in the highest risk groups.

Dr. Clay Semenkovich has demonstrated in an elegant series of experiments that, similar to cancer, atherosclerosis is mediated by genotoxic stress, broadly portrayed as the inability to repair DNA strand breaks.[3] The conceptual framework for looking at mechanisms behind genotoxic stress for clues to atherosclerosis came from the observation that children with ataxia telangiectasia, a genetic disorder due to homozygosity for the null allele of the gene know as ataxia telangiectasia mutated (ATM), develop vascular disease at a very early age, along with insulin resistance, diabetes and cancer.[4] Thus, ATM appeared to be a target for exploration of the link between genotoxic stress, atherosclerosis and insulin resistance. In a series of experiments with an atherogenic mouse model, Semenkovich and colleagues showed that ATM is a mediator of atherosclerosis, and that ATM can be activated by chloroquine, an antimalarial drug with known metabolic effects.[3] Razani and Semenkovich further demonstrated in a recent paper that the anti-atherogenic properties of chloroquine are mediated through p53 activation of ATM, but that the effect on insulin sensitivity was independent of p53.[5] Based on the earlier observations, a translational study was conducted investigating the metabolic and atherogenic effects of chloroquine given to persons with the metabolic syndrome.

The Atheroma Reduction with Chloroquine in persons with the Metabolic Syndrome (ARCH-MS), study at Washington University was recently completed (HRPO 06-0147, ClinicalTrials.gov identifiers NCT00455403 and NCT00455325). Subjects in both Aim 2 and Aim 3 met criteria for the metabolic syndrome, but were not diabetic by fasting blood glucose at screening and were not taking anti-diabetic medications. Chloroquine was studied in a dose escalation manner in Aim 2 as proof of concept that small doses given for a short period of time would reduce insulin resistance in patients with the metabolic syndrome. Results of Aim 2 demonstrated that chloroquine, taken at doses of 80 mg daily for 3 weeks and 250 mg daily for 3 weeks, reduced hepatic glucose production by 32%; and by 43% respectively, improving one of the key metabolic defects in type 2 diabetes mellitus (T2DM). There was no significant effect

on glucose disposal. The effect observed with chloroquine is similar to the metabolic effect of metformin, which is the most commonly used anti-diabetic agent and recommended as first line therapy. Aim 3 tested the effect of low dose chloroquine (80 mg per day) on progression of carotid intima medial thickness (CIMT) in a double-blind, placebo-controlled year-long clinical trial of 116 randomized participants. The chloroquine group had almost zero progression of CIMT, but this was not significantly different from the placebo group (p=0.7). Chloroquine had a non-significant effect on fasting glucose, but there was a mild reduction in glucose AUC, tested by 2-hour oral glucose tolerance test, OGTT (p=0.09). The findings from these studies have furthered our interest in clarifying whether a safe and effective agent in the quinolone class of drugs will have metabolic and possibly anti-atherogenic effects.

Hydroxychloroquine (HCQ) is an anti-malarial medication closely related to chloroquine, but more commonly used for the treatment of rheumatologic conditions including rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE).[6] It is considered to be a disease-modifying antirheumatic drug (DMARD) with pleiotrophic actions that include both anti-inflammatory and metabolic properties, neither of which are well understood.[7] In vivo and in vitro data suggests that hydroxychloroquine may have both anti-hyperglycemic and lipid-lowering actions, though well designed clinical trials testing these effects are lacking.[8]

In retrospective analyses, HCQ appears to reduce the incidence of type 2 diabetes in previously non-diabetic individuals with rheumatic conditions. Wasko and colleagues reported that non-diabetic patients with RA treated with HCQ had a significant reduction in risk of developing incident diabetes, hazard ratio 0.62 (95% CI, 0.42-0.92) compared to those not treated with HCQ.[9] Interestingly, the risk of developing T2DM was reduced with increasing duration of use of HCQ such that for those taking HCQ for more than 4 years, the adjusted relative risk of developing T2DM was 0.23 (95% CI, 0.11-0.50; P<.001).[9] More recently, Solomon and colleagues showed similar findings, a reduced relative risk of developing DM among patients prescribed HCQ or TNF inhibitor compared to other non-biologic DMARDs such as methotrexate, azathioprine and others.[10]

Hydroxychloroquine has also been shown to have a beneficial effect on glycemia in patients with T2DM. In a retrospective study of patients treated with HCQ or methotrexate for a variety of rheumatologic conditions, Rekedal found that A1c was reduced by 0.66% in those taking HCQ compared to 0.11% in those taking methotrexate (p=0.041 for the difference).[11] In a double-blind, placebo-controlled trial, Gerstein reported that HCQ, when added on to sulfonylurea treatment, improved glycemic control with a drop in glycosylated hemoglobin of 0.96% compared to placebo.[12] HCQ also prevented worsening of hyperglycemia in patients with T2DM. These findings confirmed earlier studies that reported improved glycemic control with chloroquine or HCQ in persons with T2DM .[13, 14] Both hydroxychloroquine and chloroquine have been reported to cause hypoglycemia that has on occasion been severe.[15, 16]

The metabolic effects of chloroquine and hydroxychloroquine have been studied, but are still not well characterized or understood. Powrie conducted a randomized, double blind, placebo-controlled trial in 20 patients with T2DM on no medical therapy.[17] After a baseline

hyperinsulinemic euglycemic clamp procedure with infusion of stable isotopes, 10 of the patients received 250 mg of chloroquine 4X daily for 3 days plus the morning of the repeat clamp. The other 10 patients received a placebo. Patients receiving chloroquine had a reduction in fasting plasma glucose, improvement in insulin sensitivity, and reduced clearance of insulin.[17] These effects had been previously shown in rat models.[18] In isolated kidney tubule cells and hepatocytes, chloroquine reduced gluconeogenesis in a dose dependent fashion.[19]

HCQ has also been reported to lower low-density lipoprotein.[20] Using a case-control design, van Halm et al found that the use of one or more of the DMARD agents, methotrexate (MTX), sulfasalazine (SSZ) or HCQ was associated with CVD risk reduction.[7] The mechanism behind these effects is not well understood.

HCQ has an established safety profile that permits chronic treatment. The major adverse effect is retinal toxicity, described in long-term use with both chloroquine and HCQ.[21, 22] This effect is related to the cumulative dose of either agent. Clear guidelines have been developed for ocular screening and follow-up of patients taking these agents, and were recently updated.[23] There are no reports of an interaction between chloroquine/HCQ retinal toxicity and diabetic retinopathy. Other adverse effects include neuropathy and myopathy, which are described in long-term users of the drugs and are considered rare.

The primary hypothesis of this clinical trial is that hydroxychloroquine, given in a clinically relevant dose to patients with T2DM who are taking metformin with or without other oral antihyperglycemic therapy, will reduce fasting glucose level and low density lipoprotein (LDL) . Secondarily, we will test whether hydroxychloroquine will reduce insulin resistance with the primary effect being a reduction in hepatic glucose output. Tolerance to the specified dose of 400 mg daily in divided doses will be assessed in patients taking metformin +/- other anti-diabetic medications.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome of this mechanistic clinical study is to determine whether hydroxychloroquine, compared with placebo, will reduce fasting blood glucose and/or LDL in patients with mild T2DM over a four-week treatment period.

Secondary (exploratory) outcomes are as follows:

1. To determine the effect of HCQ on insulin resistance
2. To determine the effect of HCQ on serum biomarkers of inflammation.

This clinical trial is based on the protocol for the hyperinsulinemic clamp that was used in Aim 2 of the ARCH-MS study. The basic plan of the study is to randomize otherwise healthy subjects with type 2 diabetes to hydroxychloroquine, 200 mg twice daily or placebo. All subjects will undergo fasting labs to include glucose and LDL at baseline, followed by a graded hyperinsulinemic clamp. The fasting glucose and LDL and graded hyperinsulinemic clamp will be repeated after 4 weeks of treatment along with other safety labs.

Primary and Secondary Endpoints. The primary endpoint of the protocol is reductioin in fasting glucose and LDL. Secondary endpoints include insulin sensitivity determined by hyperinsulinemic euglycemic clamp and common serum biomarkers of inflammation.

PROTOCOL PLAN

Study Design. The study is a randomized, double blind, placebo controlled clinical trial of HCQ, given 200 mg twice daily, versus placebo for 4 weeks.

Eligibility Criteria

Inclusion:

1. Subjects between the age of 18 and 75, either gender, any ethnic group
2. Subjects must have type 2 diabetes and the following:
    a. A1c of 6.5-9.0%
    b. Treated with at least 1000 mg of metformin daily with or without a DPP4 inhibitor, a sulfonylurea (glipizide, glyburide, glimepiride), bromocriptine or colesevelam.
3. Subjects should have a BMI $\geq$27

Exclusion:

1. Prior treatment with chloroquine or hydroxychloroquine as follows:
    a. any exposure in the past 2 years,
    b. >30 days of therapy if exposure was between 2 and 5 years ago,
    c. >90 days of therapy if exposure was between 5 and 10 years ago,
    d. >6 months of therapy if exposure was 10 to 20 years ago,
    e. >1 year of therapy if exposure was 20 to 30 years ago,
    f. No limit if last exposure was >30 years ago, e.g. during the Vietnam conflict.
2. Morbid obesity (BMI >45)
3. Coronary artery disease or other vascular disease
4. History of stroke
5. Serum creatinine >1.4 mg/dl for women and >1.5 mg/dl for men.
6. Seizure disorder
7. History of psoriasis
8. Hematologic disorders, including anemia (WHO criteria for anemia: hemoglobin <13 g/dL in men and <12 g/dL in women)
9. Current malignancy or active treatment for recurrence prevention, e.g. tamoxifen. Cancer considered to be cured, either as a result of surgery or other treatment is not exclusionary.
10. Asthma requiring daily beta agonist therapy or intermittent oral steroids is exclusionary. Inhaled steroids are acceptable. Obstructive sleep apnea will be allowed if CPAP or other therapy has been stable for 6 months. Other active respiratory diseases are excluded.
11. Treatment with 50mg or greater of Metoprolol or treatment with digoxin
12. Liver disease, or LFTs >2X normal
13. Active infection (including HIV)
14. Serious illness requiring ongoing medical care or medication
15. Treatment with atypical anti-psychotic medication. Treatment with any other medication for psychiatric illness, unless on a stable dose for 6 weeks prior to

enrollment. Patients with unstable psychiatric disorders are excluded per the decision of the study MD regardless of medication history.
16. Taking any of the following lipid lowering medications: niacin, fibrates, and greater than 1 gm/day of fish oils
17. Uncontrolled hypertension (BP >150/90 mm Hg) at enrollment
18. Need for daily OTC medications, or currently taking cimetidine or >1000 IU vitamin E daily and unwilling to reduce or discontinue vitamin E or discontinue cimetidine for the duration of the study. Patients taking more than 1000 IU vitamin E daily should reduce or discontinue the vitamin for 30 days before randomization.
19. Pregnant or lactating women, or women intending to become pregnant
20. Women not using adequate birth control (hormonal birth control is acceptable, also double barrier)
21. QTc >450 msec on screening ECG
22. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Study Plan and Procedures

*Screening***.** Potential subjects will be interviewed, the protocol will be explained in detail, then risks and benefits of involvement will be discussed. Those subjects interested in participating will be given ample time to review the informed consent, to ask questions of any member of the study team, and will sign the informed consent prior to any study procedures being conducted. Subjects will have a complete history and physical examination (including measurement of blood pressure according to a standard protocol and determination of height, weight and waist size) performed by experienced personnel in the Washington University IRU or by the study coordinator. A POC A1c will be performed to determine whether the patient meets the inclusion criteria. If the A1c is 6.5-9%, blood will be drawn for G6PD, CBC and CMP; and an ECG will be performed and a pregnancy test for women of childbearing potential. This visit does not require fasting. Patients who have one or more exclusions will be informed of their test results but will not proceed further. If the patient meets the inclusion and exclusion criteria specified above at the screening visit, he or she will be scheduled for fasting labs and a hyperinsulinemic-euglycemic clamp, as depicted in the schedule of events.

*Study procedures***.** Patients who provide informed consent, and who meet the inclusion and exclusion criteria will return to the study site for fasting glucose (CMP) and lipids, repeat A1c (to be done in the Core Lab), then a hyperinsulinemic-euglycemic clamp and baseline serum samples for inflammatory biomarkers will be drawn . After the clamp procedure, patients will be randomized to receive either 200 mg HCQ or matching placebo twice daily. The patients will take the study medication until the final visit, for a total duration of 4-5 weeks. The fasting glucose (CMP), lipid profile, CBC and hyperinsulinemic, euglycemic clamp will be repeated at the final visit in 4-5 weeks. Additionally, blood for biomarker profile will be drawn at the last visit. Side effects and adverse events will be monitored during the study and medication compliance assessed at the last visit. The schedule of events is shown below.

META-HCQ Schedule of Events			
Procedure	**Screening**	**Baseline Clamp**	**Follow-up Clamp**
	Week -2	Week 0	Week 4-5
Informed consent	X		
H&P	X		
Vital signs	X	X	X
ECG	X		X
POC A1c	X		
CBC, CMP	X		X
Pregnancy Test (urine) prn	X	X	X
G6PD	X		
Lab A1c		X	X
Fasting lipid profile, Biomarkers		X	X
Fasting glucose		x	X
Graded hyperinsulinemic clamp		x	X
Randomize to HCQ, 200 mg bid vs placebo bid		x	
Dispense study drug		x	
Drug accountability, return			X
Adverse events		X	X

Subjects are advised to maintain current dietary and exercise habits. Weight, BP and HR are recorded throughout the protocol.

Hyperinsulinemic-euglycemic clamps- Study patients will be asked to arrive fasting and without taking their oral anti-diabetic medications or the study medication. Two-step clamps will be performed according to a standard protocol routinely used in the Washington University IRU with hepatic glucose output determined using [6,6-^{2}H] glucose (detected by mass spectrometry in our core facility). IV lines will be started and samples for fasting glucose, c-peptide, glucagon and insulin obtained. A stable isotope-labeled glucose prime (1 mmol/m) will be given at the beginning of a 150 minute baseline equilibration period, followed by a constant infusion (0.01 mmol/m2/min . After tracer equilibration, insulin will be infused in an exponentially decreasing manner until a rate of 8 mU/m^2/min is achieved. The glucose will be clamped at 90 mg/dby altering the infusion rate of 20% dextrose based on glucose concentrations sampled from an arterialized hand vein (achieved by maintaining the hand in a heating box). The first step of the clamp will be carried out for two hours with a stable glucose infusion rate maintained for the final hour at the 8 mU/m^2/min rate. Multiple blood samples are obtained at standardized times for determination of glucose kinetics. The second step will be carried out at 40 mU/m^2/min in an analogous fashion. Potassium will be monitored during clamps and replaced appropriately. Glucose appearance rate (Ra) will be calculated from plasma tracer enrichments and rate of tracer infusion, endogenous glucose output will be calculated as Ra minus the glucose infusion

rate, and the glucose disposal rate will be calculated as glucose infusion rate plus endogenous glucose output. This visit takes 8-9 hours.

Blood tests. Most determinations will be performed by the Washington University Core Lab for Clinical Studies, a CLIA-certified facility that has served as the reference lab for landmark clinical trials including the Coronary Primary Prevention Trial and the CARE trial. The lab will measure A1c, CBC, CMP and lipid profiles including total cholesterol, HDL, triglycerides and calculated LDL at baseline and study end. Additional aliquots will be frozen for future studies of inflammatory biomarkers.

Sample Size Estimates and Statistical Analyses

The primary endpoint for this experiment is fasting glucose and fasting LDL. Insulin sensitivity determined by clamp is an exploratory aim. Based on the results of Aim 2 of the ARCH study, we expect to show a difference from baseline in fasting glucose and LDL in 15 subjects per group (80% power and α=0.05). We will therefore plan to study 15 subjects per group. We will compare differences between groups using unpaired two-tailed t tests. An interim analysis will be performed after the first 7 patients in each group have completed the study to check for significant differences or refine the sample size.

Anticipated Results, Alternative Approaches, Potential Problems and Benefits

The anticipated results of the study are that HCQ will reduce fasting glucose and will produce a small reduction in LDL. We also anticipate that HCQ will reduce glucose appearance, also known as hepatic glucose output. Based on our prior studies, no effect on blood pressure is expected. The major unknown in this study is whether HCQ at the clinically used dose of 200 mg bid will have the same effect as chloroquine. It is also not known whether HCQ will have the expected effect in the presence of metformin, since the drugs appear to have similar mechanisms of action. The LDL lowering effect of chloroquine was mild in the ARCH study, but not all patients were taking statins, and the mean LDL was higher than is commonly seen in patients with diabetes who are treated to lower LDL targets than non-diabetics. Therefore, the effect size of HCQ on LDL is unknown in this patient population. The results of this mechanistic study will be informative for the planning of future clinical trials of HCQ in persons with diabetes. The hyperinsulinemic clamp are considered to be the gold standard tests for mechanistic studies of the metabolic defects in diabetes, and thus do not have comparable alternatives.

Potential problems can occur in any clinical trial, due to the study population, the study procedures or the intervention. We plan to enroll persons with diabetes who are otherwise healthy, and who do not have G6PD deficiency, which is the major contraindication for this class of drugs. We have interrogated programs for potential drug interactions between HCQ and metformin, statins and sulfonylurea drugs, and have not discovered any. The metabolism and excretion of HCQ is not well described, so our study relies on past clinical experience in patients with rheumatologic problems.[Appendix 1] Standard safety precautions will be used for the hyperinsulinemic clamp procedures, including having a physician present for the clamp and carefully monitoring glucose levels during the studies. This procedure has been used for many

years, and is done in a very standardized fashion with safety of the patients as the top priority. Note that blood draws will be tracked for each participant so that the total amount does not exceed American Red Cross guidelines of 500 ml per 8 weeks, similar to one whole blood donation. The estimated blood loss is less than 300 ml during the entire study. Participants will be advised not to donate blood within 8 weeks of starting the study, during the study and up to 8 weeks after completion of the study.

The major adverse effect of this class of drug is retinal toxicity, which can result in vision loss. The current recommendations are to begin to monitor patients after a cumulative dose of 1000 grams, and annually thereafter.[23] This study will not enroll subjects with significant prior exposure to HCQ, and the total dose will be approximately 12-15 grams, well below recommendations for monitoring. There is no mention of an interaction between anti-malarial retinal toxicity and diabetic retinopathy, which has a different pathogenesis. Thus, specific eye examinations will not be conducted for this protocol.

Withdrawal of research subjects from the protocol may occur. Research subjects will be withdrawn if any of the following occurs:

- The patient withdraws consent for any reason
- An adverse event occurs related to study procedures (IV site problems, drop in hemoglobin, intolerance or adverse reaction to the study medication)
- An adverse event that would impact any of the study results occurs. An example would be a patient who develops poison ivy during the study and requires oral steroids for control of the rash. Efforts will be made to adjust the study schedule to permit recovery, but if that is not possible or likely, the patient will be withdrawn.

Possible benefits to study patients include satisfaction of altruistic values and a small stipend of $25 for screening visit and $175 for clamp visits, for a total of $375. All study related testing and the investigational agent will be provided at no cost.

Quality Control (Study Monitoring)

The study will be reviewed for safety, privacy and data integrity by the study investigators and staff at regular intervals during the course of the study. Safety data will be shared at regular intervals with the non-engaged safety monitors and any issues will be addressed as appropriate by PIs, sub-I, study staff and HRPO.

The PIs and/or sub-I will monitor each subject's lab results and visit data at each study visit. Subjects will be requested to contact study staff if any event occurs between clinic visits and this information will be reviewed by the PIs.

The PIs will remove any subject at his or her discretion based upon personal judgment or in the event of undue AE's. The PIs will review and report all AE's and report as per HRPO policy. Any new risks or safety issues identified will be reviewed and forwarded to HRPO for review and, if necessary, the study will be stopped. Participants will be notified of any changes that might affect their decision to participate.

Study personnel will enter subject data into a database and/or spreadsheet for analysis. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data). In all cases, subject PHI will not be collected in the database. Any information entered into databases will be stored on a secure server, which is password protected and accessible only to authorized study staff.

In accordance with applicable regulations, GCP, and HRPO requirements, the PIs will review with the study staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and HRPO requirements.

When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which a paper chart will serve as the source document. The PIs will monitor the study to ensure that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol, GCP, and all applicable regulatory requirements.

Safety and Tolerability Assessments include the following:

• AEs and SAEs

• Physical examinations, laboratory evaluations, vital sign measurements (blood pressure and pulse rate)

Study safety will be monitored by PIs and sub-I. PIs will review all reported AE's and report to HRPO, as per HRPO requirements. The PIs may halt the study participation or the study if this is determined to be in the best interest of participants. Safety Reports will be generated after 50% of patients have completed the study for review by the non-engaged study safety monitors, and reported as per HRPO policy and at least annually at the time of HRPO renewal.

Study Termination

The study will be terminated if it is determined that continuing the study would pose an unacceptable risk to subjects.

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