Pilot Study: Comparing the Effects of Hydroxychloroquine (HCQ) to Pioglitazone in Type 2 Diabetic Patients Failing Maximal Doses of Metformin Plus a Sulfonylurea

ClinicalTrials.gov NCT02303405

Protocol

Last Modified: January 11, 2017

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Background: Type 2 diabetes is characterized by insulin resistance (decreased insulin sensitivity), as well as an increased inflammatory state. It is unclear whether insulin resistance causes the inflammatory state, whether the inflammatory causes the insulin resistance, or whether each is independent of the other (Shoelson SE et al, J Clin Invest 2006; 116:1793-1801). The LA County DHS formulary for treating type 2 diabetes is currently limited to metformin, two sulfonylurea agents (SU), pioglitazone (a thiazolidinedione, or TZD) and insulin. The treatment algorithms utilized in the Diabetes Programs at the Martin Luther King Jr. Outpatient Center (MLK) and the South Central Family Health Center (SCFHC) start with metformin, after which an SU is added, and if maximum doses of both do not control patients, a maximum dose of pioglitazone is then added. We have previously published our experience with TZDs (both rosiglitazone and pioglitazone) as the third drug and found that TZDs lower HbA_{1c} levels approximately 2.0% (from a baseline value of 9.3-9.5%) with two-thirds of our patients meeting our target of <7.5% after 4 months, which avoids starting insulin at that time (Tran MT, et al. Diabetes Care 2006; 29:1395-1396). As long as HbA_{1c} levels can be maintained <7.5%, insulin is not necessary according to the treatment algorithms in the Diabetes Program at MLK-MACC. Unfortunately, although they reduce insulin resistance, TZDs may be prone to side effects including fluid retention, heart failure, weight gain, and decreased bone mineral density leading to increased fracture risk in susceptible individuals.

Hydroxychloroqinine (HCQ, Plaquenil) is an anti-inflammatory agent used to treat systemic lupus erythematosus, rheumatoid arthritis, Sjorgen's Syndrome and porphyria cutanea tardus. It has been noted that patients with rheumatoid arthritis and psoriasis taking HCQ exhibited a decreased risk for developing diabetes (Wasko MC, et al. JAMA 2007; 298:187-193; Solomon DH, et al. JAMA 2011; 305:2525-2531). These findings are consistent with isolated case reports of hypoglycemia in type 2 diabetic patients on the drug (Shojania K, et al. J. Rheumatol 1999; 26:195-196), its inclusion as a possible 3rd line agent in a review of treating type 2 diabetes (Llarde A, Tuck M. Drugs Aging 1994; 4:470-491), and its effect on decreasing glycemia in patients with type 2 diabetes (Gerstein HC, et al. Diabetes Res Clin Pract 2002;55:209-219; Rakedal LR, et al. Arthritis Rheum 2010;62:3569-3573; Quatraro A, et al. Ann Intern Med 1990;112:678-681). In a more recent study, HCQ (6.5 mg/kg) given to 13 obese non-diabetic subjects for 12 weeks significantly increased insulin sensitivity (as measured by the Matsuda Insulin Sensitivity Index) at 6 weeks with a return to baseline at 12 weeks (Mercer E, et al. Arthritis Res Ther 2012).

This pilot study will compare the efficacy of HCQ and pioglitazone (PIO) in patients who have failed maximum doses of metformin plus an SU. Ultimately, if HCQ proves to be as effective as PIO, another modality of treatment will be available with a drug that has fewer side effects. Even if HCQ is not as effective but does significantly lower HbA_{1c} levels, it may represent another drug for patients in whom PIO may be contraindicated. We also plan to monitor highly sensitive C-reactive protein (hsCRP) as a marker of inflammation, and since the anti-inflammatory properties of HCQ are well established, we anticipate that hsCRP levels will decrease. If insulin sensitivity does not improve or worsens with HCQ, we would conclude that inflammation does not contribute insulin resistance. Should both insulin resistance and

inflammation be reduced, further research would be needed to determine if the two change independently of each other or if either one could contribute to the other.

Primary Outcome: To collect preliminary data as to whether HCQ may ultimately be non-inferior to PIO in lowering HbA_{1c} levels in type 2 diabetic patients failing maximum doses of metformin and SU.
Secondary Outcomes: To collect preliminary data to eventually compare a) the percentage of patients who achieve HbA_{1c} <7.5% after receiving either HCQ or PIO for 4 months; b) the effect of PIO vs. HCQ in lowering fasting plasma glucose (FPG) and weight; and c) the effects of HCQ vs. PIO on inflammation and insulin resistance.

Research Design: A 4-month, randomized, prospective, open-label comparison trial
Subjects: Type 2 diabetic patients inadequately controlled on maximally tolerated doses of metformin plus a SU.
Recruitment: Subjects will be recruited from the Diabetes Programs at MLK and South Central Family Health Center (SCFHC). These centers serve the same large population of low-socioeconomic status and low-educational level ethnic minority patients living in the south and south-central region of Los Angeles. The diabetes clinic at MLK is staffed by the faculty of the Endocrinology Division of Charles R. Drew University of Medicine and Science, and the diabetes care providers at the SCFHC clinic were trained on the same treatment protocols by the study co-investigator. This study protocol will be reviewed by the Institutional Review Board of Charles R. Drew University prior to study initiation, and an IND application will be submitted to the FDA.
Inclusion Criteria:

- Male or female, age 18-75, inclusive
- Known type 2 diabetes (diagnosed according to 1997 ADA diagnostic criteria) receiving diabetes treatment at MLK or SCFHC
- At least 3 months of treatment with maximum tolerated doses of metformin *and* a SU, *and* inadequate glycemic control ($HbA_{1c} \geq 7.5\%$ and $< 11.0\%$)
- Body mass index (BMI) < 45 kg/m^2
- Able to comply with all scheduled visits and requirements of the protocol

Exclusion Criteria:

- Any contraindications to the use of metformin or a SU
- Extreme hyperglycemia (FPG $\geq$ 300 mg/dL), symptoms of polyuria or polydipsia, or $HbA_{1c} \geq 11.0\%$
- Current use of insulin; history or clinical suspicion of type 1 diabetes mellitus
- Symptomatic hypoglycemia occurring at an average frequency > once per day
- Highly erratic dietary schedules, extremely food insecure households, or homelessness that may adversely affect good glycemic control, as judged by the investigators
- Occupations that involve regular operation of motor vehicles or other heavy machinery that may pose a hazard in the event of unanticipated blurred vision
- Known history of Class III or IV heart failure, cardiac arrhythmias, severe peripheral edema, advanced osteoporosis, documented bladder malignancies, or other intolerance to PIO
- Known history of collagen vascular disorders, glucose-6-phosphate dehydrogenase deficiency, hematologic disorders, psoriasis, or any known intolerance to HCQ

- Known history of pre-proliferative or proliferative retinopathy, or any clinically significant retinal abnormalities noted on the patient's most recent (i.e., within 1 year) ophthalmologic exam; subjects who have not received their routine annual ophthalmologic surveillance for diabetic retinopathy within the past year must have their annual surveillance performed before screening
- An estimated GFR (by the Modification of Diet in Renal Disease (MDRD) formula) < 45 mL/min, or a history of nephrotic syndrome (defined as a spot urine protein-creatinine ratio of > 3500 mg per g urine creatinine)
- Subjects with active hemoglobin abnormalities that render the HbA_{1c} measurement unreliable
- History of any clinically significant hepatic, cardiovascular, infectious, dermatologic, psychiatric, or other major systemic disease that, in the opinion of the investigator, may make the use of PIO or HCQ unsafe, or otherwise make the interpretation of the data difficult.
- Female subjects of childbearing potential who are sexually active and not using a reliable form of contraception or do not agree to use a reliable form of contraception. Reliable forms of contraception include systemic contraceptives (oral, implant or injection), diaphragm with spermicide, cervical cap, IUD, or condoms with spermicide.
- Current pregnancy or lactation.
- Subjects who will likely require or initiate therapy with drugs that may interfere with glucose metabolism during the course of the study (e.g., glucocorticoids).
- Subjects who are in another investigational study or have received another investigational medication within 30 days of study entry
- Subjects who are unable or unwilling to give informed consent, comply with all components of the study protocol, attend all scheduled follow-up visits, or present other barriers that would make the implementation of the protocol unusually difficult.

Schedule of Procedures: This study will be approximately 4 months in duration. Subjects will be assessed at baseline, 2 and 4 months. All visits will include an assessment of:

- Fasting plasma glucose (FPG)
- HbA_{1c}
- Fasting insulin level, calculation of HOMA-IR and QUICKI indices (measures of insulin resistance; fasting insulin samples will be banked for assays to be performed in the future)
- hsCRP (samples will be banked for assays to be performed in the future), leukocyte counts (total WBC, absolute neutrophils and lymphocytes)
- Hypoglycemic symptoms (if any)
- Weight and BMI
- Any other side effects or changes in physical findings
- Compliance with all concurrent medications and study medications
- Diet and lifestyle adherence

Concurrent metformin and SU dosages will be maintained, unless down-titration of the sulfonylurea agent is necessary to prevent excessive hypoglycemia. Subjects will be advised to maintain the same dietary and activity routines throughout the course of the study.

Down-Titration of SU: In the event of new onset symptomatic hypoglycemia that is not attributable to dietary factors that are within the subject's control, the total daily dose of SU

should be reduced by 50%. If dietary factors that are within the subject's control are identified as precipitants to the hypoglycemia, then the subject should be counseled on reversing the dietary factors, and SU dose reduction may not be necessary. Interim assessments prior to the next scheduled visit (in 2 months) may be scheduled at the discretion of the investigators to assess the outcome of the counseling and/or dose reduction, and further reductions in the SU dosage may be made at the interim visits to alleviate the new onset symptomatic hypoglycemia. If the 50% dose reduction is insufficient to correct the hypoglycemia, then discontinuation of the SU may also be considered. No other changes to doses of SU will be permitted.

Screening Visit (Week 0): Consent, screening, review of inclusion and exclusion criteria, and all required subject assessments for the study will take place at the CDU CTRC. A signed authorization for the release of medical records from MLK or SCFHC for the purposes of this study will be needed from all consented subjects to permit the investigators to review the relevant results when they become available. If all entry criteria are met, blood will be taken for the following laboratory tests: CBC, electrolytes, BUN, creatinine, FPG, HbA_{1c}, AST, ALT, fasting insulin, and hsCRP; urine will be collected for a urine pregnancy test (for women of childbearing potential). For subjects from MLK, all blood and urine samples with the exception of fasting insulin and hsCRP will be drawn by the MLK outpatient phlebotomists as per the diabetes clinic's routine treatment protocols, and the investigators will retrieve those results for review when they become available; fasting insulin and hsCRP blood samples will be obtained separately by phlebotomists at the CTRC. The above laboratory tests with the exception of fasting insulin and hsCRP are not required if they have already been performed by the laboratory within the previous 4 weeks and the results are accessible to the study team. For subjects from SCFHC, any of the above laboratory test results performed within the previous 4 weeks will be requested by the investigators, and any that were not performed within the previous 4 weeks will be drawn by the CTRC (including the fasting insulin and hsCRP).

Study Medication: Subjects who satisfy all inclusion and exclusion criteria will be randomized to either PIO 45 mg once daily or HCQ 400 mg once daily (2 x 200 mg tablets). Randomization will occur based on the subject's (randomly assigned) unique medical record number issued by MLK or SCFHC: *odd numbers will receive HCQ; even numbers will receive PIO*. The study is open-label. The supply of PIO will be prescribed as per usual clinical practice through the outpatient pharmacies at MLK and SCFHC (or provided by the investigators if not obtainable from SCFHC because of their internal insurance coverage policies), and compliance will be determined by pill counts and referencing dispensing records from the MLK online pharmacy database (for subjects from MLK). The supply of HCQ will be purchased from a retail pharmacy specifically for the study, and compliance will be determined by pill counts assessed by the study coordinators at each follow-up visit. Subjects will be provided with a 90-day supply at the randomization visit so as to allow for potential variations in compliance and/or scheduling of the 2-month follow-up visit. Subjects must bring their remaining supply of unused medication at the every follow-up visit, and will be provided with a sufficient amount of additional HCQ at the 2-month visit to last until their final, 4-month visit (allowing again for potential variations in compliance and/or scheduling). Although all subjects should already have experience with the principles of dietary and lifestyle modifications as part of their ongoing diabetes therapy, these concepts will be reinforced at each follow-up visit.

Follow-Up Visits (Week 8, Week 16): Subjects will be seen at the CTRC in the fasting state, vital signs, weight and height will be taken, and blood will be drawn for FPG, HbA_{1c}, CBC, electrolytes, BUN, creatinine, AST, ALT, fasting insulin, and hsCRP. For subjects from MLK,

as with Week 0, all samples except fasting insulin and hsCRP will be obtained by the MLK phlebotomists and results will be reviewed when available; urine will be collected and processed by the MLK laboratory for a urine pregnancy test for women of childbearing potential at each follow-up visit; fasting insulin and hsCRP samples will be obtained separately at the CTRC. For subjects from SCFHC, all samples will be obtained at the CTRC (since the distance from SCFHC to CDU makes obtaining routine lab tests at SCFHC unrealistic when visits must take place at the CTRC). Based on current clinical evidence, diabetic patients are not required to perform self-glucose monitoring in the absence of insulin use, although subjects may perform self-glucose monitoring on their own if desired. Any hypoglycemic symptoms or any other adverse experiences will be reviewed and an attempt will be made to explain their occurrence. The subject's concurrent medications will be reviewed to ensure that dosages and compliance have not changed; any changes will be logged and subjects will be appropriately counseled. The entire study will last approximately 4 months.

Visit #	**1**	**2**	**3**
Week	**0**	**8**	**16**
Consent, inclusion / exclusion criteria	X		
Review of history / physical findings	X	X	X
CBC, Chemistry, FPG, HbA_{1c}, Urine pregnancy test [a] (obtained at MLK, SCFHC or CTRC)	X	X	X
Vitals, Weight, Height	X	X	X
Fasting insulin, calculation of HOMA-IR and QUICKI, hsCRP (obtained at CTRC, banked)	X	X	X
Randomization (if all criteria met)	X		
Dispense study medication supply	X	X	
Collect unused study medication supply; pill counts		X	X
Review of hypoglycemia	X	X	X
Review of adverse events		X	X
Reinforce nutrition / lifestyle	X	X	X
Review concurrent medications	X	X	X

[a] For women of childbearing potential.

Assessment Measures (performed at CTRC):

- Vital signs, height and weight will be obtained at each visit, along with a brief review of the patient's history and physical findings at week 0 to look for exclusion criteria.
- Compliance with the subject's usual nutritional and lifestyle activities will be reviewed and reinforced.
- Changes in concurrent medications will be assessed at each encounter. Every effort will be made to avoid changes in concurrent medications that may influence carbohydrate or lipid metabolism (unless down-titration of SU is required).
- Compliance with the study medication will be verified with pill counts at each follow-up visit. The need for consistent use of the study medication will be reinforced if suboptimal compliance is noted.
- Adverse events and any clinically meaningful changes in physical findings will be noted. The probability of any causal relationship between the adverse event or physical finding

and the study intervention will be judged by the investigator and if necessary, reported to the IRB.

- Hypoglycemic episodes, as defined by the presence of appropriate symptoms that are alleviated by the ingestion of carbohydrates or associated with a confirmed FPG level < 60 mg/dL, will be assessed. If necessary, subjects will be instructed on how to manage hypoglycemic reactions if they have not previously received such instructions. The frequency and timing of episodes will be noted. Possible precipitants of hypoglycemia will be reviewed and corrective measures will be advised if correctable precipitants are identified. If necessary, the subject's SU dosage may be down-titrated to alleviate any recurrent hypoglycemic episodes.

Withdrawals: Subjects may either voluntarily withdraw from the study or be withdrawn by the investigators. A subject who withdraws from the study for any reason will continue to be followed for their diabetes in their respective Diabetes Clinic after their study participation is terminated. Reasons for study withdrawal by the research team include, but are not limited to, excessive non-compliance with the study medication, repeated failure to attend scheduled visits, use of any other medications known to affect glucose or lipid control, adverse effects (including confirmed FPG ≥ 300 mg/dL or clinically significant hypoglycemia not relieved by nutritional modifications or downward titration of the SU) or any other clinical situation which, in the opinion of the investigators, may jeopardize the subject's safety.

Methodologies:

Anthropometric Measurements: Standard procedures will be followed for the measurement of vital signs, weight, height, and calculated BMI.

Laboratory Measurements: All laboratory analyses except fasting insulin and hsCRP will be obtained by the respective clinic phlebotomists specified above, and conducted by the respective clinical laboratories specified above, or the CTRC. Samples for insulin and hsCRP levels will be obtained at the CTRC, banked, and will be measured in the future by the CTRC Core Lab using commercially available RIA and/or ELISA kits: Millipore HI-14K Human Insulin RIA (Millipore, Billerica, MA); MP Biomedicals 07BC-1119 ultrasensitive CRP ELISA (MP Biochemicals, Orangeburg, NY); samples for inslin and hsCRP will remain frozen until assay reagents are available for batched runs once all samples have been collected.

Statistical Analyses:

All data will be collected onto Excel spreadsheets. Non-normal data will be log-transformed, as appropriate.

Intended Primary Endpoint: *The between-group change in the HbA_{1c} level from baseline to 4 months.*

Intended Secondary Endpoints:

A) The between-group difference in the change by 4 months of: i) % of subjects achieving HbA_{1c} < 7.5%, ii) FPG, iii) weight and BMI, iv) HOMA-IR and QUICKI, and v) hsCRP and leukocyte counts;

B) For each group, the within-group change by 4 months in HbA_{1c}, FPG, weight and BMI, HOMA-IR and QUICKI, hsCRP, and leukocyte counts;

C) The between-group difference in the incidence of i) all hypoglycemic events, ii) severe hypoglycemic events, and iii) all adverse events excluding hypoglycemia.

Analysis: Changes in all continuous outcome measures will be compared between groups using 2-way repeated measures ANOVA. A chi-square analysis will be used to compare the percent of subjects achieving HbA_{1c} <7.5% between groups. Changes within groups between baseline and

4-months will be made with one-way ANOVA. We will plan to eventually conduct both an intent-to-treat (ITT) analysis (missing data imputed using last-observation carried forward) as well as a secondary analysis of only those completed subjects with mean medication compliance ≥ 90%.

Sample Size Calculations: Due to limited available funding, as of late 2015, this pilot study alone will be unable to enroll the needed number of subjects to meet the originally intended level of statistical power; available funding accommodates enrollment of up to 60 subjects. However, the partial data obtainable using the available funding will still provide preliminary information as to a) the possibility of efficacy that may at least be similar between HCQ an PIO; b) the possibility of potentially similar effects of HCQ and PIO on secondary measures such as weight, inflammation, and insulin resistance; and c) the presence or possibility of any clinically significant safety concerns with HCQ in comparison to PIO that may be relevant to the eventual clinical use of HCQ for diabetes, or the value of pursuing future funding to complete the intended full enrollment to fully meet the study objectives. This pilot study will therefore still provide valuable preliminary data that will be critical towards eventually securing additional funding to continue the study and ultimately achieve the total enrollment target so as to draw the intended conclusions.

Data Safety Monitoring: Quarterly analyses of all accumulated safety data will be conducted, to include analyses of: a) all accumulated clinical adverse events (including the incidence of severe hypoglycemia); and b) all accumulated laboratory test abnormalities that occur after subjects have initiated their first dose of assigned study medication, and that are deemed by the investigators to represent either i) potentially clinically meaningful yet asymptomatic adverse events, or ii) clinically significant changes from baseline laboratory values that potentially represent clinically meaningful adverse events. Data collected from all enrolled subjects will be compiled by the study coordinator and reviewed and verified by the principal investigator. These cumulative data will then be presented to the CDU Data Safety Monitoring Board (DSMB, under chairperson Dr. M. Ho and any other members as deemed necessary by the DSMB, but excluding study co-investigator Dr. M. Davidson) and concurrently to the IRB. The DSMB will then review the submission independently, according to their established procedures, and report their conclusions and recommendations independently to the IRB (with a copy to the PI). Usual reporting requirements for serious and non-serious adverse events to the IRB will continue to apply throughout the study, and all such instances will also be included within each quarterly DSMB report. If on any quarterly review, the cumulative safety data indicates a possible *systematic* and clinically harmful risk that a) is likely causally related to the interventional agent and cannot be otherwise explained by subjects' concurrent circumstances, and c) cannot be mitigated by minor adjustments to the manner by which the investigators conduct or monitor subjects in the study, then consideration should be given for temporary or permanent study stoppage, with or without appropriate amendments to the protocol to mitigate the risk, as deemed necessary by the DSMB and/or IRB in consultation with the PI. Permanent study stoppage shall also be reported to the study's granting agency, as appropriate.