

Hydroxychloroquine for the Treatment of Hidradenitis Suppurativa

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1.0 Specific Aims

To evaluate the efficacy of hydroxychloroquine as a treatment for hidradenitis suppurativa (HS)
We will conduct a pilot trial of standard dosing of hydroxychloroquine in patients with HS

To identify biomarkers as possible therapeutic targets for the treatment of HS
We will evaluate the levels of inflammatory cytokines in the peripheral blood of patients with HS.

2.0 Background information

Hidradenitis suppurativa is a debilitating and mutilating disease and its pathogenesis is still poorly understood. It involves the development of recurrent, painful nodules in intertriginous areas that become inflamed, form abscesses that may rupture, and develop chronic fistula tracts. The cause of hidradenitis suppurativa (HS) is thought to be multifactorial and may begin with follicular occlusion and rupture, leading to a cascade of inflammatory responses in susceptible individuals. The disease has been associated with high body mass index, smoking and genetic predisposition. There is a known association between HS and the metabolic syndrome, an association that remains after controlling for body mass index ¹. HS predominantly affects women and ethnic minorities ^{2,3} and the prevalence is thought to be as high as 2%, although embarrassment and lack of awareness may lead to an underestimate of the true burden of disease.

Although HS is a fairly common disease, relatively little is understood about its pathogenesis. Immune dysregulation is thought to play a role in disease development. Increased levels of IL-12, IL-17 and IL-23, TNF α , IL-10 and IL-1 β were found to be expressed in lesional skin of HS patients ^{4,5}. Recent studies have also identified elevated levels of IL-17 in the serum of patients with HS ⁶.

HS is associated with a significant impact on patient quality of life ⁷. Patients suffer from both the physical and psychological impact of disease. Many therapies have been used to treat HS, from topical antibiotics to oral retinoids to radical surgeries, but all have limited efficacy. Despite efforts to control disease, many patients live with chronic wounds and disability. The decision about appropriate therapy for HS, especially in the early stages, is mainly based on expert opinion, anecdotal evidence and small studies. Topical and systemic antimicrobial treatments are often used as first line therapies, although studies have repeatedly shown that the abscesses of HS are sterile or contain only normal flora. The mechanism of improvement with antimicrobials may be through alterations in the local microbiome. Significant improvement in disease has been seen with dual therapy with twice daily use of 300mg rifampicin and 300mg clindamycin ⁸, neither of which have an FDA indication for use in HS. Doxycycline is used frequently in HS, but little evidence supports this. Despite success with the above therapies, the risk of antimicrobial resistance is real, and is increased with frequent and prolonged use of these medications in HS ⁹. Teratogenic effects, gastrointestinal upset and photosensitivity with use of tetracyclines, risk for *clostridium difficile* colitis with clindamycin, and antimicrobial resistance with rifampicin highlight a need for safer and effective therapeutic options for the treatment of early HS.

For more advanced disease (Hurley stage II and III), the tumor necrosis factor inhibitor adalimumab is the only FDA approved biologic treatment for HS. It has shown promise in severe disease, but only ~50% of patients achieved a clinical response at 12 weeks, and this clinical response declined over time ¹⁰. Additionally, newer biologic therapies have been used in small numbers of patients with HS with variable results. Importantly, the cost of these

medications is considerable.

Hydroxychloroquine, initially developed as an antimalarial, has been used successfully for over 70 years in the treatment of autoimmune disease. Its mechanism of action is still poorly understood, but it has been shown to have many varied immunomodulatory properties ¹¹. Evidence suggests that hydroxychloroquine has an effect on inflammatory disease through decreasing levels of TNF α ¹² and Th-17 cytokines (including IL-6, IL-17 and IL-22)¹³. Additionally, studies have shown a beneficial effect of hydroxychloroquine on lipid metabolism and glucose ¹⁴. Patients with rheumatoid arthritis (which similarly to HS has an independent association with cardiovascular disease) who were treated with hydroxychloroquine had an overall decreased incidence of cardiovascular events ¹⁵. Hydroxychloroquine has a relatively benign safety profile, with retinopathy being the most concerning long term side effect. The retinopathy caused by hydroxychloroquine is reversible if identified early, and standard protocols for the use of this medication include yearly ophthalmologic examination.

3.0 Experimental Design and Methods

We hypothesize that treatment with hydroxychloroquine may offer a safer and effective method to control disease activity in HS. We hypothesize that the profiling inflammatory cytokines in the peripheral blood of the patients with HS may provide novel therapeutic targets for the disease. Additionally, monitoring of inflammatory cytokines before and after treatment may help to explain the mechanism by which therapies work. Over the proposed period, we intend to gather data about patient response to treatment with hydroxychloroquine and about the cytokine profile of patients with HS. Sequential patients will be assigned to hydroxychloroquine treatment. Patients will be evaluated at baseline and after 3 months of treatment for treatment response and to evaluate quality of life measures. Serum will be collected at baseline and following 3 months of treatment. Peripheral blood from patients with HS will be analyzed for levels of cytokines thought to be involved in HS and several markers of inflammation that have not yet been analyzed in this disease.

Treatment

Patients will have baseline CBC and CMP evaluation prior to initiation of therapy
Sequential patients will be assigned treatment with hydroxychloroquine 200mg BID
Treatment length will be 3 months

Evaluation of HS

Patients will be evaluated at baseline and at 3 months by:

Hurley staging:

Stage 1: solitary or multiple, isolated abscess formation without scarring or sinus tracts

Stage 2: recurrent abscesses, single or multiple widely separated lesions, with sinus tract formation

Stage 3: diffuse or broad involvement, with multiple interconnected sinus tracts and abscesses

Number of inflammatory nodules, abscesses, fistulas, scars, locations of these lesions, longest distance between 2 relevant lesions, are lesions separated by normal skin (for Sartorius scoring)

Improvement in HS lesions

Sartorius score: A statistically significant decline in Sartorius scoring between baseline and end of treatment

Evaluation of quality of life

Patients will be asked to fill out Dermatology Life Quality Index (DLQI) survey at baseline and 3 months. It is a simple, validated 10-question questionnaire. Answers to the questionnaire will be entered into a database.

For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important

Serum for evaluation

Peripheral blood will be collected at baseline and after 3 months of treatment. A 10 ml red top tube of venous blood will be obtained from patients at the time of enrollment and at month 3 for banking and cytokine analysis. The red top tubes will be centrifuged, sera will be aliquoted, logged in the database and stored indefinitely at -80°C without identifiers by a technician in Dr. Akilov's laboratory.

Cytokine analysis

Using an inflammatory cytokine panel, levels of cytokines including L-1 β , IL-4, IL-6, IL-10, IL-17A, IL-17F, L-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN- γ , sCD40L and TNF- α will be evaluated at baseline and 3 months. Analysis will be performed at the University of Pittsburgh Cancer Institute Luminex core facility using multianalyte profiling. Levels will be compared to age, sex and BMI matched controls in our database.

Therapy may be discontinued for any of the following reasons:

Unacceptable adverse event(s),

Patient decides to withdraw from the study, or

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.0 Human Subjects

Protection of Human Subjects

Human Subjects Involvement, Characteristics, and Design. The racial, gender and ethnic characteristics of the proposed subject population will reflect the demographics of Pittsburgh and the surrounding area and/or the patient population of the UPMC Health Systems. We shall attempt to recruit subjects in respective proportions to these demographics. No exclusion criteria will be based on race, ethnicity, gender, or socioeconomic status. The numbers of enrolled male to female subjects will be consistent with and reflective of the numbers of patients seen in the UPMCHS clinics and in approximate 1:1 proportion.

Sources of material.

Information on the subject's medical history will be obtained relative to the inclusion and exclusion criteria. Data collection methods will include data obtained specifically for research purposes based on the most recent office note. All records related to this research study will be stored in a locked file cabinet. The subject's identity on these records will be indicated by a case number rather than by name, and the information linking these case numbers will be kept separate from the research records.

Recruitment

Potential subjects with Hurley stage I/II hidradenitis suppurativa will be identified by the

examining physician and referred for evaluation by the principal investigator or co-investigator. Subjects will be recruited from the UPMC dermatology department clinics. Potential subjects will be evaluated by the Principal Investigator, who is also the treating physician, during a routine clinic visit prior to any screening procedures or evaluation of the medical record for research purposes. Potential subjects will be approached by physicians directly involved in their care. No “cold calling” will occur. Informed consent will be obtained on all subjects by the principal investigator prior to all screening procedures. If for any reason, a subject is excluded or resigns during the course of study, a new subject will be enrolled.

Inclusion Criteria

Enrolled HS patients must be Hurley stage I or II (defined above)

Patients may be on topical therapy only, and/or have completed non-immunosuppressive therapy at time of enrollment.

Subjects must be 18 years of age and must be able to understand the written informed consent.

No evidence of active infection, regardless of the degree of severity or localization. Subjects with active infections (whether or not they require antibiotic therapy) may be eligible after complete resolution of the infection. Subjects on antibiotic therapy must be off antibiotics for at least 7 days before beginning treatment.

Exclusion criteria

Subjects currently on systemic immunosuppression are ineligible

Subjects under 18 years of age

Due to small risk of retinopathy, hepatic disease, psoriasis exacerbation, exacerbation of porphyria cutanea tarda (PCT) in patients treated with hydroxychloroquine, subjects with known retinal disease, hepatic disease, psoriasis and PCT will be excluded

Due to potential fetal risk with use of hydroxychloroquine, pregnant patients or those planning to become pregnant will be excluded

Risks to the subjects:

- i. The risks of the study are minimal and are related drug therapy and to obtaining the blood samples needed for our analysis.
 1. Physical.
 - a) Small likelihood of drug toxicity. Hydroxychloroquine has been used for many years and is known to have a mild side effect profile.
 - b) Small likelihood of infection or bleeding. Risks minimized by proper protective equipment and hygiene
 2. Psychological. There is a small likelihood of low psychological risk if participants are upset by request to be involved in the study

7. Benefits

- i. Benefits may accrue to patients with HS. Benefits may accrue to study subjects who participate through greater awareness leading to greater individual and community empowerment, enhanced knowledge of community assets as well as health concerns and needs, and enhanced skills related to performance of duties as study subjects. Outside of participants in research, all community members may also benefit from enhanced trust and reciprocity within the community.

5.0 Statistical considerations

1. Sample size

- i. The study will involve 20 patients with hidradenitis suppurativa
- ii. The comparison of baseline Sartorius scores and level of the measured cytokines in peripheral blood from HS will be compared using a two-sided t test with a p value <0.05 for statistical significance.
- iii. The probability is 80% that the study will detect a difference at a two-sided 0.05 significance level if the true difference between groups is 30%.

6.0 Adverse Reaction Reporting Requirements:

This study will use the CTC version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0. All Serious Adverse events that require reporting to the FDA will be reported on the FDA 3500 medwatch form found in Appendix B

- i. The following adverse reactions must be reported in the manner described below.
- ii. All adverse events which are considered to be related to the research study must be reported to the University of Pittsburgh Cancer Institute (UPCI)
- iii. All serious adverse events that meet the University of Pittsburgh Institutional Review Board's criteria for reporting can be found at (<http://irb.pitt.edu>)

	Unexpected, fatal or life threatening and associated with study drug	Unexpected, of moderate or greater severity (But not fatal or life threatening) and are associated with the research intervention	Serious, unexpected event that is associated with the study drug	Unexpected fatal or life-threatening experience which is associated with the study drug
Call to UPCI within 24 hours at (412) 647-8074	X			
Notify IRB within 24 hours	X			
Notify UPCI as soon as		X		

possible & local IRB within 10 days				
FDA notification within 15 days			X	
FDA notification within 7 days				X

An adverse reaction is considered *serious* if it is fatal or life-threatening; requires or prolongs hospitalization; produces a disability; or results in a congenital anomaly/birth defect.

An adverse reaction is considered to be of *moderate or greater severity* if it requires medical evaluation (such as additional laboratory testing) and/or medical treatment; or if it is a serious adverse reaction.

An adverse reaction is considered to be *unexpected* if it is not identified in nature, severity or frequency in the current IRB-approved research protocol or informed consent document.

An adverse reaction is considered to be *associated with the research intervention* if there is a reasonable possibility that the reaction may have been caused by the research intervention (i.e., a causal relationship between the reaction and research intervention cannot be ruled out by the investigators).

UPCI requires ADRs to be reported on the Medwatch form and on the University of Pittsburgh IRB adverse event form. The University of Pittsburgh Adverse event form must be signed by the treating investigator.

(See Appendix A for copies of the Adverse event reporting forms).

iv. FDA Guidelines for Adverse Event Reporting

All adverse events meeting the definition of serious, unexpected and associated to the research intervention will be reported to the IRB according to their guidelines found at (<http://irb.pitt.edu>):

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

Life threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

7.0 Reporting of results

Following acquisition of the descriptive data and the calculation of formal statistics, manuscript(s) will be prepared for submission to peer reviewed journals.

8.0 Costs and Payments

Neither subject, nor their insurance provider, will be charged for the costs of any of the procedures performed for the sole purpose of this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring Procedures described above). Subjects will be charged, in the standard manner, for any procedures performed for their routine medical care.

References

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