Oral Low-Dose Naltrexone in the Treatment of Lichen Planopilaris and Frontal Fibrosing Alopecia; an uncontrolled open-label prospective study.

Principal Investigator:

Caroline Mann, MD

NCT01109041

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A Introduction

A1 Study Abstract

Oral naltrexone was initially FDA approved to treat opioid use disorder and alcohol dependence at doses from 50-100mg/day. At lower doses of 1-5mg/day, naltrexone has been used off-label with success in treatment of several dermatologic conditions including the scarring alopecia (irreversible hair loss), lichen planopilaris. A recent case series of four patients with lichen planopilaris and a subtype, frontal fibrosing alopecia, treated with oral low-dose naltrexone at 3mg daily showed reduction of itch, clinical evidence of inflammation of the scalp, and of disease progression. There were no reported adverse events.

Based on the promising evidence, we propose using low-dose naltrexone at a daily dose of 3mg to treat lichen planopilaris and frontal fibrosing alopecia. The patients would be continued on their other medications for these conditions. The study would be open-label, so all participants would receive the low-dose naltrexone. Patients would be seen at monthly intervals over a period of six months to monitor their progress.

A2 Primary Hypothesis

Does daily oral low-dose naltrexone (3mg per day) reduce symptoms and disease progression in patients with lichen planopilaris and frontal fibrosing alopecia?

A3 Purpose of the Study Protocol

To outline background and procedures relating to this study.

B Background

B1 Prior Literature and Studies

Mechanism

Naltrexone is an opioid antagonist with multiple systemic pathway effects, including those involved in pruritus, wound healing, and immune system homeostasis.[1] Low-dose oral naltrexone (doses 1-5mg daily) exhibits partial binding to μ, κ, and δ opioid receptors, which induces a paradoxical increase in opioid receptor expression as well as of endogenous opioids, β-endorphins, and methione-enkephalin.[1, 2] In addition to effects on the opioid receptors, naltrexone also acts as an antagonist on Toll-like receptor 4, thereby producing anti-inflammatory effects through reduction of tumor necrosis factor-α, interleukin-6, and nitric oxide.[2] The effectiveness of naltrexone is attributed to the widespread distribution of opioids and their receptors in the cutaneous neuroendocrine system.[1]

Background

Lichen planopilaris (LPP) is an inflammatory, cicatricial alopecia, of which frontal fibrosing alopecia is considered a clinical variant.[3, 4] Clinical features of LPP include perifollicular erythema and scaling leading to destruction of follicular ostia and patchy scarring alopecia. In the frontal fibrosing alopecia variant, hair loss occurs on the frontotermporal region, often with associated eyebrow loss. Symptoms include pruritus, burning, pain, and tenderness. Treatment options are limited and yield inconsistent results.[3] High potency topical steroids and topical tacrolimus are recommended as first line therapies for primary cicatricial alopecias.[3] However, topical corticosteroids may be less effective in FFA.[5] Other frequently utilized treatments include intralesional triamcinolone acetonide and topical minoxidil.[3] Hydroxychloroquine[6] and doxycycline are often used as systemic treatments in both LPP and FFA, whereas finasteride/dutasteride have been reported successfully in FFA.[3, 7] Overall, the level of evidence for the above treatments is limited to level IV or V evidence, and further studies into this scarring disease are needed.[8]

Oral naltrexone is FDA approved to treat opioid dependence and alcohol use disorder at doses from 50-100mg/day. At lower doses of 1-5mg/day, naltrexone has been used off-label with success in treatment of several dermatologic conditions including lichen planopilaris. A recent case series of four patients with lichen planopilaris and a subtype, frontal fibrosing alopecia, treated with oral low-dose naltrexone at 3mg daily showed reduction of pruritus, clinical evidence of scalp inflammation, and of disease progression.[3]

While initial studies using LDN for dermatologic conditions is promising, the level of evidence is low, generally limited to case reports and series. Recently, three excellent summaries of evidence for naltrexone in dermatologic conditions have been published.[1, 2, 9] A recent review article of therapy for FFA includes naltrexone at 3 mg/day in their FFA treatment algorithm.[7]

LDN maintain stability and efficacy through 90 days when crushed into water. One method of dosing is to crush ten 50mg tablets of naltrexone (500mg total) into 500 mL of water or juice, thus creating a 1mg/mL solution. This can be shaken prior to dispensing. At the time of reporting, this solution cost about $15.[10]

B2 Rationale for this Study

While initial studies using LDN for dermatologic conditions is promising, the level of evidence is low, generally limited to case reports and series. Based on case reports, we expect the participant to benefit though decrease in their symptoms (burning, itching) as well as decreased redness and scale and possibly slowing or halting disease progression.
This increased data would benefit society by providing further evidence for the use of low-dose naltrexone in lichen planopilaris and frontal fibrosing alopecia.

C Study Objectives

C1 Primary Aim

Based on case reports, we expect the participant to benefit though decrease in their symptoms (burning, itching) as well as decreased redness and scale and possibly slowing or halting disease progression.

C2 Rationale for the Selection of Outcome Measures

A recent case series of four patients with lichen planopilaris and a subtype, frontal fibrosing alopecia, treated with oral low-dose naltrexone at 3mg daily showed reduction of pruritus, clinical evidence of scalp inflammation, and of disease progression.[3]

D Investigational Agent

D1 Preclinical Data

D2 Clinical Data to Date

D3 Dose Rationale and Risk/Benefits

See section B above.

E Study Design

E1 Overview or Design Summary

Uncontrolled open-label prospective study

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Adults age 18 or greater with clinically or histologically confirmed diagnosis of lichen planopilaris or frontal fibrosing alopecia are eligible.

2.a Exclusion Criteria

Patients with known allergy or hypersensitivity to naltrexone will be excluded. Patients will be screened for opioid use with urine screen for opioids, and any patients with positive test or concurrent use of opioids will be excluded from the study. Postmarketing reports of suicidal thoughts, attempted suicide and depression have been reported with high dose naltrexone. While no reports of mood changes have been reported with low-dose naltrexone, patients will be counseled to report any mood changes that arise during

their treatment. Patients with currently active depression, schizophrenia, and bipolar disorder will be excluded.

2.b Ethical Considerations

Eligeable subjects may take naltrexone without enrolling in the study to eliminate coercion.

2.c Subject Recruitment Plans and Consent Process

Patients will be recruited from the pool of patients seen at Washington University/BJH dermatology clinics with existing and new diagnoses of lichen planopilaris and frontal fibrosing alopecia. Recruitment will be by word of mouth. Participants will be adequately informed about the study and have an opportunity to ask questions prior to enrollment. They will be seen during routine dermatology clinic visits and evaluated per protocol to determine eligibility for the study. Patients will have an opportunity to read and take home the consent form. Enrollment will be on a rolling basis between September 1st and October 31st, 2019. Patients who enroll in the study will be followed in Dr. Caroline Mann's dermatology clinic at 969 North Mason Road (BJH West County). We will confirm with patients that they have decision-making capacity and the ability to understand the risks and benefits of the treatment.

Patients who do not respond to the invitation to participate in the study will be contacted at the phone number in their medical record to address any questions they may have and to confirm whether or not they will participate. Opt-out procedures include verbally indicating that they do not wish to participate.

Study participants will receive a copy of the consent document for their records. Participants will be given a signed copy of the consent document. This will be provided to them at the time of signing. The form will also be scanned into their electronic medical record.

2.d Randomization Method and Blinding

N/A, not randomized

2.e Risks and Benefits

Based on case reports, we expect the participant to benefit though decrease in their symptoms (burning, itching) as well as decreased redness and scale and possibly slowing or halting disease progression.
This increased data would benefit society by providing further evidence for the use of low-dose naltrexone in lichen planopilaris and frontal fibrosing alopecia.

Use of naltrexone in patients on long-term opioids may induce opioid withdrawal, so patients will be screened for opioid use. Additionally, as LDN upregulates the number of opioid receptors, patients must be cautioned that this can potentiate the effect of opioid agonists, leading to risk of opioid overdose.[1] Patients will be advised that if they require emergent pain control for other conditions, opioid alternatives should be considered or if

opioids are required, they are administered under the direct supervision of a physician. While long-term safety data are not available, side effects with low-dose naltrexone are minimal, not significantly different from placebo, and include vivid dreams, nightmares, and headaches.[1] Morning dosing of low-dose naltrexone can decrease these effects, if present.[2] Based on studies involving retrospective chart reviews of patients treated with LDN for multiple sclerosis and Crohn's disease without significant laboratory abnormality, Lee and Elston concluded that no laboratory testing is required in the absence of specific signs or symptoms.[2] Postmarketing reports of suicidal thoughts, attempted suicide and depression have been reported with high dose naltrexone. While no reports of mood changes have been reported with low-dose naltrexone, patients will be counseled to report any mood changes that arise during their treatment.

2.f Early Withdrawal of Subjects

Subjects may withdraw by telling the study team they are no longer interested in participating in the study or by sending a withdrawl letter. The investigator may also decide to end participation due to patient becoming ineligeable (see eligibility criteria above) or due to unforeseen safety issues.

2.g When and How to Withdraw Subjects

Subjects will be contacted be phone or in person at a routine office visit.

2.h Data Collection and Follow-up for Withdrawn Subjects

All data obtained prior to withdrawal will be included in the data analysis.

E3 Study Drug

3.a Description

Naltrexone

3.b Treatment Regimen

Low dose naltrexone at 3mg PO daily.

3.c Method for Assigning Subjects to Treatment Groups

N/A: open-label, non-randomized, uncontrolled study

3.d Preparation and Administration of Study Drug

Will be compounded by a compounding pharmacy.

3.e Subject Compliance Monitoring

Will be reviewed at regular follow-up visits at 0,3,6 and 12 months.

3.f Prior and Concomitant Therapy

Low-dose naltrexone, 3mg orally to be taken daily, will be prescribed. They will be continued on their other treatment medications for lichen planopilaris (LPP) and frontal

fibrosing alopecia (FFA) during the study period without increasing dose. During the study period, other LPP and FFA medications may be decreased in dose or discontinued, but will not be increased or added. This will allow the investigators to analyze the specific benefit of naltrexone.

3.g Packaging

As per compounding pharmacy.

3.h Blinding of Study Drug

N/A

F Study Procedures

F1 Screening for Eligibility

This will be performed at a routine office visit prior to enrolling in the study.

F2 Schedule of Measurements

Performed at 0,3,6, and 12 month office visits.

F3 Visits

At each office visit, data will be collected as outlined on the patient assessment form. We will confirm with patients that they are not taking opioids medications and that their mood is stable without evidence of depression. Additionally, patients will be asked about any adverse reactions that they might notice from the medication, specifically inquiring about vivid dreams, nightmares, and headaches, as well as any other side effects they have noticed with the medication. The study will begin between September 1st and October 31st 2019 and continue until December 31st 2020.

F4 Safety and Adverse Events

Patients will be screened at each office visit. In addition, they will be encouraged to report any concerns or issues to Dr. Caroline Mann at the contact information listed on the consent form.

4.a Definitions of Adverse Events

Reported adverse events with low-dose naltrexone are rare and mild. Vivid dreams, nightmares, and headaches have been reported with low-dose naltrexone used for other conditions. A recent case series of four patients with lichen planopilaris and a subtype, frontal fibrosing alopecia, treated with oral low-dose naltrexone at 3mg daily showed

reduction of itch, clinical evidence of inflammation of the scalp, and of disease progression. There were no reported adverse events.

4.b Data Collection Procedures for Adverse Events

All adverse events will be recorded in the patient's medical record as well as on a secure document (Excel spreadsheet in Wustl Box) and will be reviewed monthly by the study team.

4.c Reporting Procedures

Subjects may report in person or by telephone at any time during the study.

4.d Adverse Event Reporting Period

September 1st 2019 and December 31st, 2020

4.e Post-study Adverse Event

Patients may report post-study adverse to Dr. Caroline Mann at any time after the study is completed.

G Statistical Plan

Longitudinal data from time points at 0,3,6 and 12 months will be analyzed for each component of the data collection form, including components of the patient assessment of itch and burning/pain (each on a 0-10 point scale), physician assessment for erythema and scale (each on a 0-3 scale) as well as longitudinal comparisons of measurement of the scalp involvement (distance in cm from the glabella to hairline in FFA, and area of scarring/redness/scaling in cm2 for LPP). See below for data collection form.

We predict that oral low-dose naltrexone would lead to approximately 2-3 point decrease in each of the 0-10 point patient assessments (itch and burning/pain) and a 1-2 point decrease in each of the 0-3 point physician assessments (erythema and scale). We expect the areas of scalp involvement to remain stable over the analysis period.

Patient characteristics will be summarized using descriptive statistics. The longitudinal outcomes will be analyzed using mixed model analysis to account for the correlation of measures from the same subject. Time effect will be assessed and contrasts will be used to compare mean difference between any two time points of interest. All statistical tests will be two-sided with a significance level of 0.05 and performed with SAS 9.4. Careful attention will be paid to ensuring that data satisfy assumptions required of a particular analytic strategy. When required assumptions are violated, we will explore the use of data transformations and potentially, perform some analyses using non-parametric or semi-parametric methods based on the rank of some variables.

Data on the quantitative effect size of naltrexone for LPP/FFA is limited, but based on clinical experience and descriptive case studies, we would expect patients to start at a 4-5/10 on the itch/pain/burning scales, and predict that it could decrease to 1-2/10 with

naltrexone treatment. Similarly, we expect that patients would start at a 1-2/3 on the physician assessments (erythema and scale) and predict that the physician assessments of erythema and scale could decrease to a 0-1/3. Finally, we expect the areas of scalp involvement to remain stable over the analysis period. Based on existing data showing low number of mild side effects and no serious adverse events, we plan to enroll 75-100 patients, which is the maximum number that we would expect to see over the study period given the low prevalence of disease.

With estimated standard deviation using a rule of thumb based on range of the scales, the anticipated 75-100 patients can achieve at least 80% power to detect mean difference of 0.7-0.8 based on patient assessment as well as 0.21-0.25 based on physician assessment. Therefore, the anticipated sample size is sufficient to detect the expected effects. The power was based on two-sided paired t-test comparing before and after treatment at significance level 0.05.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Data will be kept in the patient's medical record or in secure files in Wustl Box. Persons that have access to the medical record will be able to view data. Only the investigators of this study will have access to the secure files in Wustl Box.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

None.

I2 Auditing and Inspecting

None.

J Study Administration

J1 Organization and Participating Centers

Washington University in St. Louis.

J2 Funding Source and Conflicts of Interest

Funding from the WashU division of Dermatology. No conflicts of interest.

K Publication Plan

Plan to submit for publication in Spring 2020.

L Attachments

L1 Tables

Data collection sheet.

L2 Informed consent documents

The above are attached as part of the IRB.

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