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A study looking at the mechanism of action of a drug called disulfiram in patients with Ocular Fibrosis in Mucous Membrane Pemphigoid (OcMMP)

Submission date
17/07/2024

Recruitment status
Recruiting

Registration date
12/09/2024

Overall study status
Ongoing

Last Edited
18/03/2025

Condition category
Eye Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Conjunctival scarring results from many diseases. These include trachoma, an infection that is known to be the largest cause of preventable blindness worldwide. It causes irreversible sight loss in both eyes in 1.9 million people worldwide. In the UK, the most common cause is a rare autoimmune-driven disorder called Ocular Mucous Membrane Pemphigoid (OcMMP) that occurs in 0.8 people per one million of the population each year. OcMMP creates chronic inflammation and scarring of the conjunctiva which lines the inside of the eyelids and covers the white of the eye. Scarring of the inside lining of the eyelid can cause the lashes to turn inwards and scratch the cornea (trichiasis). This and inflammation, lead to debilitating symptoms of constant irritation, pain, and dryness. Treatments involve immunosuppression but this has little effect on scarring. For half of patients, scar formation continues; 20% become irreversibly blind. Aldehyde Dehydrogenase (ALDH) is thought to drive this scarring process. Disulfiram is a drug given by mouth as an alcohol deterrent treatment which permanently blocks ALDH action. We would like to understand whether disulfiram has the same impact if given to patients with OcMMP. As there is no licensed disulfiram eyedrop formulation, we would like to give tablets by mouth at the UK-licensed safe dose, to patients with OcMMP for two weeks and examine how it affects the scarring signals in the conjunctiva.

Who can participate?
Patients aged 16 years or older, with persistent ocular inflammation.

What does the study involve?
We will give tablets by mouth at the UK licensed safe dose, to patients with OcMMP for two weeks and examine how it affects the scarring signals in the conjunctiva. We will do this by taking swabs, tear, blood and faecal samples from patients before starting treatment, one week into treatment, at the end of treatment and during the 2-week period after coming off treatment.

What are the possible benefits and risks of participating?
Benefits:
There may be no benefit to you from participating in this study, but the possible benefits include:
• The repurposed oral disulfiram drug may hamper the inflammation and scarring process driving the progression of your condition.
• If this study shows promising results, your involvement directly helps in driving this kind of treatment into mainstream use where it may help treat both yourselves and others like you who may also suffer from OcMMP and other ocular scarring disorders
Risks:
• Possible side effects from taking Disulfiram –this is unlikely to be above the standard effects of taking this tablet in a standard-of-care setting. In the absence of any alcohol ingestion, the most common symptoms include Headaches and a metallic taste in the mouth. Other known side effects include allergic dermatitis, breath odour, depression, drowsiness, encephalopathy, fatigue, hepatocellular injury, decreased libido, mania, nausea, nerve disorders, paranoia, psychotic disorders, and vomiting. Participants will be monitored throughout the study period by the clinical team and will be informed if any significant new information becomes available regarding the study medication. Daily virtual clinics at home will be conducted to monitor patient safety in between hospital clinic visits.
• Disulfiram is a medication used in the treatment of alcohol use disorders. It works by producing unpleasant side effects and sensitivity to alcohol. When taken with alcohol the drug is known to cause a number of different side effects including a condition called 'disulfiram-alcohol reaction' which can be severe and may cause chest pain, nausea, flushing, dizziness, low or high blood pressure, decreased respiration, a fast heartbeat, coma and convulsions. If you take part in this study, it is therefore very important that you do not consume, and avoid contact with, alcohol.
• The treatment may not be effective- to minimise this risk, patients are allowed to use their regular eye drop treatments alongside the study treatments. The study will look at whether using Disulfiram tablets alleviates symptoms. Daily virtual clinics will also be conducted whilst the participant is on treatment to ensure safety monitoring.
• The participant diary and virtual clinics will be used to ensure treatment adherence is maintained by participants and the diary will be reviewed by the clinical study team at each clinic visit to ensure compliance.
• The virtual clinics will be conducted daily whilst the participant is on treatment to monitor safety, and the site will also complete a concomitant medication form detailing all medication the participant is taking.
• The Ocular Mucous Membrane Pemphigoid symptoms may get worse - patients will be followed up regularly by the clinical team and are free to withdraw at any time if they wish to do so.
• Attending multiple hospital visits- this may be a burden for patients, but we are doing it for safety reasons to monitor eye health. Taxis can be arranged for transportation and travel fees will be reimbursed. Our Patient and Public Involvement (PPI) group feedback highlighted that the visit burden was concerning for patients and in response we reduced the number of clinic visits (adding virtual reviews to the schedule) and increased the time between clinic visits.
• Time taken to complete the tests and questionnaires during the visits may be tiring - the durations are explained in the participant information sheet (PIS) and visit lengths have been reduced in accordance with patient feedback. Patients have the option to be transported via taxis so that they do not have to drive home.
• Slight discomfort from some of the tests - some tests involve applying liquid to the eye (e.g. fluorescein dye), collecting samples from the eye and taking blood samples. The discomfort is explained in the PIS and most of the procedures are done as part of the standard care for patients with Ocular Mucous Membrane Pemphigoid so will not be new to them.
• Personal data recorded on all documents will be regarded as confidential and will be handled and stored in a secure environment and in accordance with GDPR, GCP and the Data Protection

Act 2018.
Participants will be identified using only their unique trial number and initials on the Case Report Form (CRF) and correspondence between the MMP-Oral-DSF Trial Office and the participating site. Date of birth may be used in correspondence between the Site and the MMP-Oral-DSF Trial Office, where appropriate to aid in correct participant identification. This is fully explained in the PIS.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
July 2024 to September 2028

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
MMP-Oral-DSF Trial Manager, MMP-Oral-DSF@trials.bham.ac.uk

Contact information

Type(s)
Principal Investigator

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Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1009671

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RG_22-122, CPMS 61464

Study information

Scientific Title
Impact of Oral Disulfiram on Aldehyde Dehydrogenase (ALDH) Mediated Ocular Fibrosis in Mucous Membrane Pemphigoid (OcMMP). An experimental medicine study evaluating oral disulfiram repurposed to probe the ALDH mediated profibrotic mechanism in ocular disease (MMP-Oral-DSF)

Acronym
MMP-Oral-DSF

Study objectives
Primary objective:
To evaluate the inhibition of ALDH activity in tears to confirm pharmacological engagement of disulfiram (DSF) in the eye (reduction in ALDH activity).

Secondary objectives:
To evaluate oral disulfiram is associated with a reduction in:
1. A reduction in Collagen Type 1 and Type 3, Fibronectin and Thrombospondin expression in the conjunctiva
2. A reduction in ocular surface proinflammatory cytokine profile
3. Changes that are sustained after intervention withdrawal

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 30/08/2024, London - Chelsea Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8141; chelsea.rec@hra.nhs.uk), ref: 24/LO/0588

Study design
Interventional non randomized

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Mucous Membrane Pemphigoid (MMP)

Interventions
This is an experimental medicine study (primary outcomes are mechanistic) with one Study Arm called the Disulfiram (DSF) Arm. Ten participants in Stage 1 will undergo a 42-day study period, incorporating a pre-treatment phase (14 days), a 14-day treatment phase (single loading dose of 600 mg of oral disulfiram followed by a daily dose of 200 mg for a further 13 days), and a post-treatment surveillance phase (14 days) during which time samples will be taken for mechanistic analyses at 7 time points. If tolerability limits are exceeded, the daily dose will be reduced to 100 mg once daily and if this dose is not tolerated in at least 4 in 10 patients, the study will be stopped as not tolerable. If oral disulfiram is shown to be tolerable and ALDH activity is shown to be reduced in at least 1 participant eye during interim analysis, Stage 2 of the study will be deployed, and a further 20 participants will be recruited to follow the same 42-day study design, including the 14-day dosing regimen.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic, Therapy

Phase
Phase 0

Drug/device/biological/vaccine name(s)
Disulfiram

Primary outcome measure
Response in the eye defined as a reduction in ocular surface ALDH activity by >=50%, measured in tear washings. Also, a response in the patient defined as a reduction in systematic ALDH activity by >=50% measured in serum. ALDH Activity PicoProbe™ fluorometric assay conducted on both tear washings and serum. This demonstrates disulfiram and/or active metabolite penetrates the eye and inhibits the target enzyme ALDH (measured in tear washings). NB

inhibition of blood ALDH activity confirms adherence to the intervention. The difference in ALDH Activity from baseline to 14 days after treatment starts will be calculated and any eye or patient (in tear washing, serum, respectively) with at least a 50% reduction will be considered to have responded to treatment. Any eye /patient with less than a 50% reduction in activity will be considered a non-responder. To be done after all 10 patients have been recruited to stage 1 then after all 20 patients have been recruited to stage 2.

Secondary outcome measures

Current secondary outcome measures as of 30/12/2024:
Multiple endpoints are to be evaluated during the study. The primary timepoint for comparison is day 14 compared to day 0 (baseline).
In addition, multiple biological samples are taken throughout the study at defined timepoints between screening and day 28. This will allow additional analytical comparisons to be made which include all sample timepoints.
1. Inhibition of ALDH-mediated profibrotic gene expression signalling by >=50%: Polyester swabs to assess ocular surface gene expression (quantified via Nanostring fibrosis panel) and Collagen Type 1 protein expression (quantified via ELISA). Data will demonstrate normalising gene expression supportive of ocular surface and tear function (Profibrotic: COL3A1, FN1 and THBS1; Ocular surface function: SCIN, HMGS2, and XCL1/2) and Collagen Type 1 protein expression. As for the primary outcome measure, a 50% or greater reduction in the expression of genes COL3A1, FN1, and THBS1, as well as collagen type 1 protein expression will be assessed at day 14 post-treatment with the baseline levels.

Previous secondary outcome measures:
Multiple endpoints to be evaluated during the study. The primary timepoint for comparison is day 14 compared to day 0 (baseline).
In addition, multiple biological samples are taken throughout the study at defined timepoints between screening and day 28. This will allow additional analytical comparisons to be made which include all sample timepoints.
1. Inhibition of ALDH-mediated profibrotic gene expression signalling by >=50%: Polyester swabs to assess ocular surface gene expression (quantified via Nanostring fibrosis panel) and Collagen Type 1 protein expression (quantified via ELISA). Data will demonstrate normalising gene expression supportive of ocular surface and tear function (Profibrotic: COL3A1, FN1 and THBS1; Ocular surface function: SCIN, HMGS2, and XCL1/2) and Collagen Type 1 protein expression. As for the primary outcome measure, a 50% or greater reduction in the expression of genes COL3A1, FN1, and THBS1, as well as collagen type 1 protein expression will be assessed at day 14 post-treatment with the baseline levels. The definitions of responders and non-responders are the same as described for the primary outcome measure
2. Reduction in ALDH-mediated production of proinflammatory and profibrotic factors on the ocular surface and systemically. Custom Luminex Bioassay™ performed on both tear washings and serum samples will be performed. Custom readouts include: IL-1, IL-2, IL-4, IL-5, IL-6, IL-13, IFNγ, TNFα,EGF, TGFβ1, VEGF, PDGF, MMP8, MMP9, HSP47, Neutrophil Collagenase, Gelatinase, Myeloperoxidase, Collagen Type 1
3. Prolonged inhibition of ALDH in tear washings and serum after treatment is stopped will be assessed on days 21 and 28 by determining the number and proportion of eyes and participants that meet the definition of responding to treatment as described for the primary outcome who were recorded as responders at day 14

Overall study start date

15/07/2024

Completion date
30/09/2028

Eligibility

Key inclusion criteria
1. Aged ≥16 years
2. Persistent ocular inflammation (CCAT score ≥2 for >3 months) and evolving scarring
3. No change in systemic or ocular therapy for >3 months prior to enrolment, and not likely to change physician-directed standard care management over the course of the 42-day study period

Participant type(s)
Patient

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
30

Key exclusion criteria
Current exclusion criteria as of 27/09/2024:
1. Planned surgery involving the eyelid/ conjunctiva including eyelid repair surgery, oral mucosal grafting to reconstruct fornix, or tarsorrhaphy during the course of the study (surgery can be performed after the 42-day study).
2. Patients not willing to abstain or refrain from alcohol consumption 14 days pre-, during and 14 days post treatment.
3. Any history of liver disease, Or alanine transaminase (ALT) >2.5x upper limit of normal, OR bilirubin >1.5x upper limit of normal at screening.
4. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
5. Recent diagnosis of or unstable cardiac failure (within last 6 months)
6. History of cerebrovascular accidents
7. Uncontrolled hypertension
8. Known coronary artery disease
9. Recent admission to hospital related to poorly controlled diabetes (e.g. diabetic ketoacidosis or recurrent hypoglycaemic episodes requiring hospital attendance) within the last 6 months.
10. Active seasonal allergic conjunctivitis (hay fever)
11. Presence of active ophthalmic infection: bacterial, fungal or viral
12. Presence of persistent infective corneal ulcers or current eye condition impacting on the study as judged by a clinician
13. Known hypersensitivity to any of the components of the study or procedural medication
14. History of drug, medication or alcohol abuse or addiction
15. Unable to understand, speak and write the English language

16. Use of any investigational agent within 4 weeks of study entry
17. Participation in another investigational medicinal product (IMP) or ophthalmic interventional clinical trial at the same time as the present study
18. Participant has received a live attenuated vaccine within 30 days of study entry
19. Participants on an unstable dose of antidepressants or not willing to stay on the same dose throughout the study duration
20. Participants on an unstable standard daily dose of inhaled steroids or not willing to stay on the same dose throughout the study duration PRN may differ but the standard daily dose prescribed must not vary).
21. Participants who are not willing or able to adhere to study procedures and/or schedule
22. Participants with evidence of significant acute or chronic medical or psychiatric condition including severe personality disorder, suicidal risk, psychosis, or anything that, in the judgement of the investigator, would compromise the participant's safety or ability to complete the study.
23. Participants who are currently pregnant or breast-feeding
24. Females of child-bearing potential who do not agree to use a highly effective method of birth control (plus barrier methods) during heterosexual intercourse from screening until 2 days after last study treatment
25. Females of childbearing potential using hormonal contraception for less than 3 months prior to study entry, or using hormonal contraception and not willing to stay on it for the duration of study
26. Females taking Hormone Replacement Therapy (HRT) not willing to remain on treatment for the study duration or have started HRT within the last 3 months prior to study entry or are on an unstable dose of HRT
27. Male, if not vasectomised, who does not agree to use barrier method plus a highly effective method of contraception during heterosexual intercourse from screening through to 2 days after the last dose of study treatment.

Previous exclusion criteria:
1. Planned surgery involving the eyelid/ conjunctiva including eyelid repair surgery, oral mucosal grafting to reconstruct fornix, or tarsorrhaphy during the course of the study (surgery can be performed after the 42-day study).
2. Patients not willing to abstain or refrain from alcohol consumption 14 days pre-, during and 14 days post treatment.
3. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
4. Recent diagnosis of or unstable cardiac failure (within last 6 months)
5. Recent diagnosis of Cerebrovascular accidents (within last 6 months)
6. Recent hypertensive crisis or diagnosis of malignant hypertension (within last 6 months)
7. Unstable coronary artery disease (within the last 6 months)
8. Recent admission to hospital related to poorly controlled diabetes (e.g. diabetic ketoacidosis or recurrent hypoglycaemic episodes requiring hospital attendance) within the last 6 months
9. Active seasonal allergic conjunctivitis (hay fever)
10. Presence of active ophthalmic infection: bacterial, fungal or viral
11. Presence of persistent infective corneal ulcers or current eye condition impacting on the study as judged by a clinician
12. Known hypersensitivity to any of the components of the study or procedural medication
13. History of drug, medication or alcohol abuse or addiction
14. Unable to understand, speak and write the English language
15. Use of any investigational agent within 4 weeks of study entry
16. Participation in another investigational medicinal product (IMP) or ophthalmic interventional clinical trial at the same time as the present study
17. Participant has received a live attenuated vaccine within 30 days of study entry

18. Participants on an unstable dose of antidepressants or not willing to stay on the same dose throughout the study duration
19. Participants on an unstable standard daily dose of inhaled steroids or not willing to stay on the same dose throughout the study duration PRN may differ but the standard daily dose prescribed must not vary).
20. Participants who are not willing or able to adhere to study procedures and/or schedule
21. Participants with evidence of significant acute or chronic medical or psychiatric condition that, in the judgement of the investigator, would compromise the participant's safety or ability to complete the study
22. Participants who are currently pregnant or breast-feeding
23. A woman of child-bearing potential (WOCBP) who does not agree to use a method of birth control (including barrier methods) during heterosexual intercourse from screening until 1 day after last study treatment
24. Females of childbearing potential using hormonal contraception for less than 3 months prior to study entry, or using hormonal contraception and not willing to stay on it for the duration of study
25. Females taking Hormone Replacement Therapy (HRT) not willing to remain on treatment for the study duration or have started HRT within the last 3 months prior to study entry or are on an unstable dose of HRT
26. Male, if not vasectomised, who does not agree to use barrier contraception (condom) during heterosexual intercourse from screening through to 1 day after the last dose of study treatment.

Date of first enrolment
04/12/2024

Date of final enrolment
04/08/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Birmingham Midland Eye Centre (BMEC)
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Sponsor type
University/education

Website
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ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer-reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities

Intention to publish date
31/05/2029

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the CRUK clinical trials unit in accordance with the CRCTU data sharing policy: https://www.birmingham.ac.uk/research/crctu/Data-sharing-policy.aspx . Any request to access clinical trial data needs to be requested in writing via the CRCTU data sharing request form. This data will only be made available after the full analysis of the study data has been undertaken and published in addition to the generation of a complete study report.

IPD sharing plan summary
Available on request