An exploratory, single-center, two-part study to describe mycosis fungoides characteristics and explore novel biomarkers with a multi-modal patient profiling approach by comparing MF patients to healthy volunteers

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Primary- To evaluate disease-related characteristics and biomarkers in patients with mycosis fungoides compared to healthy volunteers; Secondary- To evaluate the variability of the selected biomarkers between patients and within patients over time...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON52201

Source
ToetsingOnline

Brief title
Deep phenotyping of CTCL, type mycosis fungoides

Condition

- Epidermal and dermal conditions

Synonym
Blood cancer affecting the skin

Research involving

Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR funded study,Recordati

Intervention

Keyword: CTCL, Mycosis fungoides, Phenotyping

Outcome measures

Primary outcome

This study will monitor the changes over time of selected biomarkers. For clinical applicability, a biomarker should be comparable over time and distinctive within the selected study groups (healthy/MF-patients and lesional/non-lesional). Due to the exploratory nature of this study, a major primary endpoint is missing. Furthermore, based on developments in analysis or based on results, additional analysis on the taken samples could be added in the future. The following general endpoints have been defined, with the groups defined as early-stage MF-patients and healthy volunteers.

* Comparable biomarker measurements (as described below under endpoints) over time and within groups for the observational part of the study
* Difference in non-invasive and/or invasive biomarker measurements between different groups (that ultimately could lead to improved disease classification)
* MF subgroups (responders vs non-responders): change in any of the invasive and/or non-invasive biomarkers after 16 weeks of treatment with CL gel compared to measurements of untreated/non-lesional skin

Secondary outcome

N.v.t.

Study description

Background summary

In recent years, knowledge about the wide spectrum of cutaneous T-cell lymphomas (CTCL) has broadened. Mycosis fungoides (MF) comprises about 50-70% of all primary cutaneous T-cell lymphomas (Willemze et al, 2019). Many CTCL are misdiagnosed due to clinical and histopathological similarity to other skin conditions (such as psoriasis vulgaris, atopic dermatitis and tinea corpora), low prevalence of disease and a lack of reliable tools for detection of these diseases, resulting in delayed diagnosis with years of discomfort and possibly a worse prognosis. Furthermore, standard treatment has never been proven curative, has many side effects and exacerbations are frequent. To date, the etiology of mycosis fungoides remains unknown and little research has been conducted into the mechanisms underlying its development and its response to treatment.

Mycosis fungoides lesions change over time and differ between patients, consisting of three morphologically different stages: patches (erythematosquamous maculae), plaques (erythematosquamous, elevated and occasionally infiltrated lesions) and tumors (with or without ulceration). Only a relatively small group of patients advances to tumor stage MF during their lifetime. Mycosis fungoides is diagnosed by correlating clinical appearance with histopathological analysis of an invasive skin punch biopsy. Additionally, often multiple biopsies are required after diagnosis, e.g. when a lesion is clinically advancing to a different stage or if lesion origin is ambiguous. Currently no other biomarkers besides skin punch biopsies markers are available for the diagnosis of MF, the evaluation of a MF lesion over time, and the monitoring of a potential treatment effect. To advance MF patient care and the development of novel treatments for MF objective, sensitive and reliable (preferably non-invasive) tools are desired.

Therefore, the objective of the current study is to phenotype the early stages of mycosis fungoides in detail and to assess chlormethine (CL) gel monotherapy. With this approach we aim to detect novel biomarkers and to establish methodologies for the (non-)invasive monitoring of MF.

Study objective

Primary

- To evaluate disease-related characteristics and biomarkers in patients with mycosis fungoides compared to healthy volunteers;

Secondary
- To evaluate the variability of the selected biomarkers between patients and within patients over time.
- To evaluate biomarkers for disease-monitoring following CL gel treatment
- To investigate and monitor skin-related AEs that might develop after CL gel application in MF patients

Study design

This is a single-center, two-part, combined observational and interventional study.

Intervention

Chlormethine gel 0.016%, thrice weekly the first 4 weeks followed by once daily for the next 12 weeks

Study burden and risks

The overall aim of this study is to evaluate objectively measured disease related characteristics to comprehensively characterize patients with mycosis fungoides compared to healthy volunteers.

Benefit
No medical benefit can be expected during the observational part of this study for the participating subjects. For MF-patients continuing in the interventional part, partial to complete mSWAT response may be expected for 63.3% of the patients after 12 months of treatment (including the optional extension protocol). Partial to complete response by CAILS may be expected for approximately 25% of the patients after 16 weeks of treatment and for 76.7% after CL gel treatment for 12 months (Lessin et al., 2013). It is important to note that in case of partial response patient can continue CL treatment after EOS in an outpatient setting.

Risks
Albeit all study procedures are considered minimal invasive, participants can experience pain and/or haematoma and in rare cases local infection during and after a punch biopsy and/or venepuncture. Both biopsies and suction blisters can possibly leave a lasting mark on the skin, therefore healthy subjects with a history of hypertrophic scarring or keloid will be excluded. Furthermore, patients could experience a (temporary) flare-up of disease related symptoms and lesions due to interruption of their standard treatment. Drug-related skin AEs are to be expected in 62% of the treated patients, of which local skin

irritation (20%), itch (18%) and erythema (16%) are most frequently observed. Additionally, these AEs are frequently anticipated and mitigated in the outpatient clinic. Drug-related skin AEs are managed according to table 2. Reference is made to the SmPC for an overview of AEs and associated treatment related risks.

Contacts

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Scientific
Centre for Human Drug Research

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy volunteers must meet all of the following inclusion criteria:
1. Signed informed consent prior to any study-mandated procedure;
2. Male or female subjects, 18 to 75 years of age, inclusive at screening; in general, stable good health as per judgement of the investigator based upon the results of a medical history, physical examination, vital signs, ECG and

laboratory assessments performed at screening. Repeated laboratory testing may be performed at the discretion of the clinical investigators;
3. Body mass index (BMI) >= 18.0 and <= 40.0 kg/m2; during COVID-19 pandemic only >= 18.0 and <= 33.0 kg/m2
4. No clinically significant skin disease as judged by the investigator
5. No history of hypertrophic scarring or keloid.
6. Subject is willing to refrain from extensively washing (including bathing, swimming, showering and excessive sweating) the skin 4 hours before every study visit.
7. Subject is willing and able to washout and withhold any topical treatment (prescription and over the counter products) in the treatment area (if possible matched location to most common location of target lesions of the MF group, and otherwise 100cm2 on the lower back) for 2 weeks prior to Day 1.
8. Subject is willing to refrain from application of any topical product (e.g. ointments, crème or washing lotions) on the skin 24 hours prior to every study visit day.
9. Subject is willing and able to washout (topical and oral) antibiotic therapy for 14 days prior to Day 1.
10. Subject is willing to use effective contraception from screening until EOS if subject is male or women of childbearing potential
11. Subject has the ability to communicate well with the investigator in the Dutch language and is willing to comply with the study restrictions.

Eligible MF patients must meet all of the following inclusion criteria at screening:
1. Signed informed consent prior to any study-mandated procedure;
2. Male or female subjects, 18 to 75 years of age, inclusive at screening; in general, stable good health as per judgement of the investigator based upon the results of a medical history, physical examination, vital signs, ECG and laboratory assessments performed at screening. Repeated laboratory testing may be performed at the discretion of the clinical investigators
3. Body mass index (BMI) >= 18.0 and <= 40.0 kg/m2; during COVID-19 pandemic only >= 18.0 and <= 33.0 kg/m2.
4. At least one patch and/or plaque lesion present, with at least one dimension with a diameter of >= 6cm.
5. Confirmed MF-diagnosis (stage 1a/1b) by histology (or clinico-histopathological correlation) within the last 10 years.
6. Willing and able to washout any topical treatment for MF (at least 2 weeks) and any systemic treatment for MF (at least 4 weeks) prior to Day 1, resulting in a washout of 8 weeks for topical treatment and 10 weeks for disease-related systemic treatment prior to the first dosing day (day 43).
7. No previous use of CL gel (Ledaga) in the past two years.
8. Subject is willing and able to washout (topical and oral) antibiotic therapy for 14 days prior to Day 1.
9. Subject is willing to refrain from extensively washing (including bathing, swimming, showering and excessive sweating) the skin 6 hours before every study visit day and up to 2 hours after application of the treatment gel.

10. Subject is willing to use effective contraception during the study if subject is male or women of child bearing potential, for up to 90 days after the last dose of study treatment
11. Male subjects must be willing to withhold from any sperm donation during the study and up to 90 days after the last dose of study treatment

Exclusion criteria

Eligible healthy volunteers must meet none of the following exclusion criteria at screening:
1. History of immunological abnormality (e.g., immune suppression) that may interfere with study objectives, in the opinion of the investigator.
2. The use of systemic antibiotic therapy for >2 months the past 12 months.
3. The use of any oral/systemic medication (e.g. immunomodulatory, immunosuppressive) within 28 days prior to Day 1, if the investigator judges that it may interfere with the study objectives.
4. Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV ab), or human immunodeficiency virus antibody (HIV ab) at screening;
5. Participation in an investigational drug study within 3 months prior to screening or more than 4 times a year.
6. Loss or donation of blood over 500mL within three months prior to screening.
7. History of alcohol consumption exceeding 5 standard drinks per day on average within 3 months of screening. Alcohol consumption will be prohibited from at least 24 hours preceding each study visit.
8. Positive urine test for drugs or history of abuse at screening or pre-dose. Urine drug test may be repeated at the discretion of the investigator;
9. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding;
10. Any other known factor, condition, or disease that might interfere with study conduct or interpretation.

Eligible MF-patients must meet none of the abovementioned and following exclusion criteria at screening:
1. Have any current relevant skin infections/disease in the treatment area other than the observational disease (mycosis fungoides), inclusively, but not limited to atopic dermatitis, psoriasis vulgaris, dermatomycosis and other skin malignancies.
2. Having received treatments for MF or any other disease within the following intervals prior to the start of the study (The use of topical emollients is allowed during the study. For target lesions it is allowed up to 24h before every study visit day):

a. < 2 weeks for topical treatment, e.g. corticosteroids, retinoids, vitamin D analogs
b. <4 weeks for phototherapy, e.g. UVB, PUVA, PDT

c. <4 weeks for non-biologic systemic treatment, e.g. retinoids, methotrexate
d. <6 weeks for peginterferon alfa-2a
e. <8 weeks for radiotherapy or surgery in the treatment area
f. <3 months for any systemic chemotherapeutical treatment
3. Known hypersensitivity to chlormethine gel or its excipients

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-10-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	chlormethine hydrochloride
Generic name:	chlormethine hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	05-07-2021
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22372

Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-001576-41-NL
CCMO	NL77292.056.21
Other	NL9764 and NCT05303480
OMON	NL-OMON22372