An exploratory, multi-centre, two-part study to describe chronic induced urticaria characteristics and explore novel biomarkers with a multimodal patient profiling approach by comparing CIndU patients to chronic spontaneous urticaria patients and healthy volunteers

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Ethical review	Approved WMO
Status	Pending
Health condition type	Angioedema and urticaria
Study type	Observational invasive

Summary

ID

NL-OMON56483

Source
ToetsingOnline

Brief title
Deep phenotyping of CIndU

Condition

- Angioedema and urticaria

Synonym
Chronic inducible urticaria, Symptomatic dermographism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic inducible urticaria, Cold urticaria, Omalizumab, Symptomatic dermographism

Outcome measures

Primary outcome

Primary endpoints for the primary objectives:

• Blood-based biomarkers (including but not limited to abs. eosinophil counts,

abs. basophil counts, C-reactive protein, total serum IgE, D-dimer, complement

assessement, basophil activation test , IgG-anti-Fc*RI, cytokine profile

assessment)

• Skin punch biopsies:

o Histology

o Spatial metabolomics

o Tissue CyTOF

o Transcriptomics

Secondary outcome

• To evaluate biomarkers for disease-monitoring during standard of care

treatment with omalizumab and at follow-up;

• To evaluate the response of the biomarkers and disease characteristics to

standard of care treatment with omalizumab.

• To explore the variability of the selected biomarkers between patients and within patients over time during and in relation to standard of care treatment (omalizumab);

• To explore and determine the different endotypes of cold urticaria and symptomatic dermographism.

Secondary endpoints:

• Provocations test: TempTest®, FricTest®

• Swab of healthy skin and (non-) lesional skin for microbiome

• Faecal microbiota

• Antera 3D multispectral imaging (3D skin morphology, erythema, haemoglobin and melanin levels)

• Laser speckle contrast imaging (microcirculation)

• 2D photography

• ePRO (Electronic patient reported outcomes): UAS7, UCT, DLQI, SDAS, SD-Qol, Cold-UAS, Coldu-QOL

• Withing watch

• Skin barrier assessment by Nevisense

• Stratum corneum sampling with tape stripping

Study description

Background summary

Chronic inducible urticaria (CIndU) is a group of skin disorders defined by recurrent itchy or burning wheals or angioedema that recur for more than six weeks with a specific triggering factor. This is different from chronic spontaneous urticaria which does not have a specific triggering factor. CIndU is subclassified in nine subtypes with each having its own specific trigger. These subtypes are further divided in physical urticarias (symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema) or non-physical urticarias, i.e., cholinergic urticaria, aquagenic urticaria, and contact urticaria.

Symptomatic dermographism (SD) is the most prevalent subtype of the physical urticarias. Its prevalence in Western populations is estimated to be between 1-5%. Following SD, cold urticaria (ColdU) is the next most common form, its annual incidence is estimated to be 0.05%. In this study, patients with the ColdU and symptomatic SD subtypes will be enrolled.
As of yet, disease diagnosis of SD and ColdU is mostly purely clinical (clinical picture + patients* history), as there is a lack of objective biomarkers. Currently only two objective tools are available for the diagnosis of SD and ColdU, which are the FricTest and Temptest (both provocation tests). In addition, there is a lack of objective biomarkers for the prediction of treatment response and for the monitoring of treatment effects, as this is nowadays only monitored by patient reported outcomes.

The objective of this study is to deep phenotype CIndU (subtype SD and ColdU) and detect novel biomarkers for diagnosis and treatment response as well as establish methodologies for (non-) invasive monitoring of treatment effects in chronic inducible urticaria.

For this purpose, a study with a multi-modal approach will be performed for in-depth characterization of SD and ColdU. The study will consist of 2 parts: in part A the biology of disease will be investigated, and in part B the response of the biomarkers to real-world treatment with omalizumab will be monitored (part B). The former to characterize objectively measured disease characteristics and mechanisms underlying its development, the latter to monitor response of the disease and its characteristics to standard of care treatment once in four weeks. The study focusses on cellular, molecular, biophysical, imaging and microbiome analyses in comparison with chronic spontaneous urticaria (CSU) patients and matched healthy volunteers.

Study objective

The objective of this study is to deep phenotype CIndU (subtype SD and ColdU) and detect novel biomarkers for diagnosis and treatment response as well as establish methodologies for (non-) invasive monitoring of treatment effects in

chronic inducible urticaria.

The primary objectives are:
• To evaluate disease-related characteristics and biomarkers in patients with CIndU compared to CSU patients and healthy volunteers;
• To evaluate the variability of the selected biomarkers between patients and within patients over time during and in relation to standard of care treatment (omalizumab);
• To evaluate and determine the different endotypes of cold urticaria and symptomatic dermographism.

Study design

This is a two-part, observational study. In part A 10 healthy volunteers, 10 CSU patients,10 ColdU and 10 SD patients will be included. All patients will visit the EMC Rotterdam or the UMC Utrecht for a screening visit and two short visits (day 1 and day 15 (end of observational period)). All healthy volunteers will visit CHDR for a screening and 2 short visit (day 1 and day 15 (end of study)).
Patients will continue the study with part B, in which standard of care treatment with omalizumab will be administered every 4 weeks during a 12 week treatment period. There will be 4 study visits in part B followed by one follow-up visit.

Study burden and risks

Omalizumab treatment:
Omalizumab is an humanized ant-IgE monoclonal antibody with a positive benefit/risk ratio for the use in chronic urticaria (CSU and CIndU). A detailed explanation of the potential issues of concern is therefore not included as the EMA assessment report for omalizumab suffices.

Study procedures:
Biopsies with a size of four millimeter in diameter are taken in order to assess histology, immunohistochemistry and perform imaging mass cytometry analysis from one biopsy. Biopsies of this small size generally do not need stitching in order to heal. Biopsy can possibly leave a lasting mark on the skin, therefore healthy subjects with a history of hypertrophic scarring or keloid will be excluded. The biopsy are performed at day 1 (for patients and healthy volunteers) and at EOS for patients. Results from these time points will provide a comprehensive overview on how disease characteristics and biomarkers of lesional skin will change when treatment effects are apparent compared to non-responding skin. Healthy volunteers will only undergo a single biopsy and blister at day 1 as they will only participate in the observational part.

In summary, the risk to participate in the trial can be assessed as acceptable.

Contacts

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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. Male and female subjects between 18-69 years of age; in general, stable good health as per judgement of the investigator based upon the results of a medical history, physical examination and vital signs.
2. No clinically significant skin disease in the research area
3. No history of hypertrophic scarring or keloid.
4. Willing to give written informed consent and willing and able to comply with the study protocol.
5. Body mass index (BMI) > 18.0 and < 35 kg/m2.

6. Negative TempTest and FricTest at screening.
7. Participant is willing to refrain from extensively washing (including bathing, swimming, showering and excessive sweating) the skin 12 hours before study visit 1.

Eligible patients must meet all of the following inclusion criteria at screening:
8. Male and female subjects between 18-69 years old
9. Diagnosis of SD, ColdU or CSU (moderate to severe according to international guidelines (Zuberbier et al, 2022)) for >=3 months and symptomatic disease despite treatment with H1 antihistamines (up to fourfold the approved dose).
10. Patients currently on an antihistamine (up to fourfold the approved dose) must be on a stable dose for at least 2 weeks prior to day 1 and must maintain the same stable dose throughout the treatment period. Patients are according to the stepped care model
eligible to start treatment with omalizumab.
11. Body mass index (BMI) > 18.0 and < 35.0 kg/m2.
12. Willing to give written informed consent and willing and able to comply with the study protocol.
13. Positive provocation test:
a) For ColdU patients: developing a wheal at the test site within 10 min after using TempTest® at any temperature at both screening and Baseline;
b) For SD patients: developing a wheal at the test site within 10 min after using FricTest® with >= 3mm at both screening and Baseline.
14. For CSU patients: negative TempTest® and FricTest® at screening
15. Participant is willing to refrain from extensively washing (including bathing, swimming, showering and excessive sweating) the skin 12 hours prior to Day 1 and EOS.
16. Female participants of reproductive potential must agree to use contraception from screening until EOS.

Exclusion criteria

General for all subjects to be enrolled:
1. Significant, uncontrolled or unstable disease in any organ system as per judgment of the investigator (regardless of association with the immunosuppressing disorder/therapy), including but not limited to: psychiatric, neurologic, cardiovascular, pulmonary, gastrointestinal, hepatic, renal, endocrine, hematologic or respiratory disease.
2. History of immunological abnormality (e.g., immune suppression) that may interfere with study objectives, in the opinion of the investigator.
3. Loss or donation of blood over 500 mL within three months prior to screening.
4. Positive hepatitis B surface antigen (HbsAg), hepatitis C antibody (HCV ab), or human immunodeficiency virus antibody (HIB ab) at screening (healthy

volunteers only)
5. Known infection requiring (topical or oral) antibiotic therapy within 56 days prior to Day 1.
6. The use of systemic antibiotic therapy for >2 months the past 12 months.
7. 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.
8. Treatment with omalizumab within 5 half lives (120 days) prior to Day 1.
9. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding.
10. Have any current and/or recurrent clinically significant or subject reported skin condition other than the CInDU/CSU wherefore subject is included in the study.
11. Evidence of current drug or alcohol abuse.
12. History of regular alcohol consumption within 12 months of the trial defined as an average weekly intake of >21 alcoholic drinks/week for men or >14 alcoholic drinks/week for women (i.e., 1 drink is equivalent to 150 mL of wine or 360 mL of beer or 45 mL of hard liquor).

Eligible healthy volunteers must not meet the following exclusion criterion at screening:
13. Participation in an investigational drug study within 3 months prior to screening or more than 4 times a year.

Eligible patients must meet none of the following exclusion criteria at screening:
14. For CIndu patients: active CSU or other forms of CIndU besides ColdU or SD that may interfere with study assessments. For CSU patients: presence of active CIndU Disease that may interfere with study assessments.
15. Urticarial or angioedema symptoms such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1 inhibitor deficiency).
16. Active, pruritic skin condition in addition to CIndU (CIndU patients) or CSU (CSU patients).
17. Routine doses of the following medications within 30 days prior to Day 1: Systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide.
18. Intravenous (IV) immunoglobulin G (IVIG), or plasmapheresis within 30 days prior to screening.
19. Regular (daily/every other day) doxepin (oral) use within 6 weeks prior to Day 1.
20. Any H2 antihistamine use within 7 days prior to screening.
21. Any leukotriene receptor antagonist (LTRA) (montelukast or zafirlukast) within 7 days prior to Day 1.
22. Patients with current malignancy, history of malignancy, or currently under work-up for suspected malignancy except non-melanoma skin cancer that has been treated or excised and is considered resolved.

23. Hypersensitivity to omalizumab or any component of the formulation.
24. History of anaphylactic shock.
25. Evidence of parasitic infection.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-10-2023
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	03-11-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-08-2024
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL84908.058.23