Rediscovery of metformin for the chronic disabling auto-inflammatory disease hidradenitis suppurativa

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The primary objective of this study is to determine the clinical efficacy of doxycycline and metformin compared with the standard treatment with doxycycline alone after 24 weeks of treatment.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin appendage conditions
Study type	Interventional

Summary

ID

NL-OMON50983

Source
ToetsingOnline

Brief title
Metformin in HS

Condition

- Skin appendage conditions

Synonym
Acne inversa, Verneuil's disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Subsidie ZonMw Goed Gebruik Geneesmiddelen Rediscovery

Intervention

Keyword: Diabetes, Hidradenitis Suppurativa, Treatment

Outcome measures

Primary outcome

The primary endpoint is the difference in International Hidradenitis

Suppurativa Severity Score System (IHS4) between the groups at week 24.

Secondary outcome

Patient reported outcome measures:

• Change in skin related pain on a numerical rating scale from baseline and

differences between the groups at week 12 and 24.

• Change in self-reported frequency of flares from baseline and differences

between the groups at week 12 and 24.

• Change in quality of life measures with the DLQI and EQ-5D-5L from baseline

and differences between the groups at week 12 and 24.

• Treatment satisfaction and recommendation on a 5- and 3-point Likert scale

respectively after 12 and 24 weeks

Clinical efficacy

• Change in lesion count from baseline and differences between the groups at

week 12 and 24.

• The percentage of HiSCR achievers after 12 and 24 weeks

• The percentage of modified HiSCR achievers after 12 and 24 weeks

• The percentage of patients with a reduction in HS-PGA from baseline and

differences between the groups at week 12 and 24. after 12 and 24

weeks

Insulin resistance and metabolic syndrome

• Change in insulin resistance measured with the HOMA-IR from baseline and differences between the groups at week 12 and 24.

• Change in HbA1c after from baseline and differences between the groups at week 12 and 24.

• Change in parameters of metabolic syndrome (waist circumference, blood pressure, HDL cholesterol, and triglycerides) from baseline and differences between the groups at week 12 and 24.

Cost-effectiveness

• Cost-effectiveness of both treatments

Biomarker:

• The correlation between baseline calprotectin levels and baseline disease severity.

• The correlation between calprotectin levels and treatment response at week 12 and 24.

Safety and tolerability:

• Incidence and severity of all adverse events throughout the study

Study description

Background summary

Hidradenitis suppurativa (HS) is a chronic, immune-mediated inflammatory skin disease characterised by painful inflammatory nodules and abscesses. Risk factors are female gender, a family history of HS, smoking, and overweight or obesity. The latter factors together with the high inflammatory load in HS lead to a high concomitant disease burden of metabolic syndrome and (pre)diabetes. A meta-analysis showed an odds ratio of 2.85 for diabetes (95%CI 1.34-6.08) and an odds ratio of 2.22 for metabolic syndrome (95%CI 1·62-3.06) in patients with HS compared with healthy controls.

Current guidelines for the treatment of this debilitating disease recommend treatment cycles with antibiotics with anti-inflammatory properties.However, patients often suffer from gastro-intestinal side effects and yeast infections, and rightfully worry about antibiotic resistance. Based on the pathogenesis of HS other systemic treatments with anti-inflammatory properties are potential candidates to alleviate HS symptoms, indicating that we should broaden our scope beyond antibiotics.

In the past years the evidence for the immunomodulatory properties of metformin has been mounting. A growing body of evidence suggests that metformin affects key immunological functions of T- and B-lymphocytes, and macrophages, cells implicated in HS pathogenesis.

This provides a strong rationale for the treatment of HS with metformin. An open label, pilot study with metformin has been performed in HS.21 In this study 18 out of 25 patients noticed a clinically meaningful improvement with an average reduction in Sartorius score of 7.6 points (SD 11.2) after 12 weeks of treatment, with an additional reduction of 5.1 points after prolonged treatment, reaching a total reduction of 12.8 points (SD 11.3) after 24 weeks. Minimal side effects were noted. A recent retrospective study (n=53) showed that metformin could be given for prolonged periods of time while being well tolerated. This study also highlighted the high prevalence of (pre-diabetic) insulin resistance (75%) among HS patients, but no validated clinical outcome measure was used. However, the important additional benefit of metformin in reducing insulin resistance in these patients was not assessed. If proven effective in a prospective RCT, metformin could be the first treatment for moderate HS which also reduces one of the most common comorbidities in this population: insulin resistance.

Study objective

The primary objective of this study is to determine the clinical efficacy of doxycycline and metformin compared with the standard treatment with doxycycline

alone after 24 weeks of treatment.

Study design

A 24-week, two arm, multicentre, double-blind, randomised controlled trial with an add-on design in patients with mild to moderate hidradenitis suppurativa.

Intervention

Group A will receive doxycycline 100mg once a day for the duration of 24 weeks. Group B will receive a combination of doxycycline 100mg once a day plus metformin for the duration of the study. Metformin will be up-titrated from a starting dose of 500mg a day in the first week, through 1000mg a day in week 2, to a maximum of 1500mg a day from week 3 onwards. Group A will additionally be given a placebo in the same dosing regimen as metformin to ensure blinding between groups.

Study burden and risks

Patients will visit the hospital every 6 weeks for a duration of 24 weeks. Venapuncture will be performed at every visit requiring patients to be fasting for at least 6 hours. In addition patients will fill out questionnaires at every visit. Doxycycline is currently a first line treatment for HS with known efficacy. It is well tolerated and has an acceptable side-effect profile, mainly comprised of gastro-intestinal side effects, increased sensitivity to sunlight, and vaginal candidiasis among women. Metformin has shown promise as a treatment for HS with the most common side effect being transient gastro-intestinal complaints at the start of treatment. To reduce the gastro-intestinal symptoms we will up-titrate the dose of metformin slowly over the course of 3 weeks.

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

• Age >=18 years at baseline
• A diagnosis of HS for at least 1 year prior to baseline
• mild to moderately active disease defined by a HS Physician Global Assessment (HS-PGA)
score of 2-3 and the Refined Hurley classification of mild to moderate
at baseline
• Indication for systemic therapy; i.e. uncontrolled disease under conventional topical therapy.
• Able and willing to give written informed consent and to comply with the study requirements.

Exclusion criteria

• Pregnant and lactating women
• Previously diagnosed diabetes mellitus and receiving active treatment
• Use of oral antibiotics within 14 days prior to baseline
• Use of immunosuppressing/modulating therapies within 28 days prior to baseline
• A known allergy to metformin or doxycycline or any of the ingredients metformin or doxycycline
• Contraindications for the use of either metformin (e.g. acute metabolic acidosis, or severe
kidney failure with a creatinine clearance < 30 ml/min) or doxycycline (severe liver function
disorders)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-09-2021
Enrollment:	62
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-03-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-05-2021
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2020-005271-12-NL
CCMO	NL75745.078.20
Other	NL9050