Effectiveness of adalimumab combined with adjuvant surgery versus adalimumab monotherapy in the treatment of hidradenitis suppurativa.

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The primary objective of this prospective study is to assess the clinical efficacy of the combination of adalimumab and surgery compared to adalimumab monotherapy after one year of treatment in adult patients with moderate to severe HS at the last…

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

Summary

ID

NL-OMON50218

Source
ToetsingOnline

Brief title
HS-COST

Condition

- Skin appendage conditions
- Skin and subcutaneous tissue therapeutic procedures

Synonym
acne inversa

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adalimumab, en bloc excision, Hidradenitis Suppurativa

Outcome measures

Primary outcome

The main endpoint of this study is the change in IHS4 (delta IHS4) at the last visit (12 months or the last visit before dropout). The IHS4 is calculated by the following formula: Inflammatory nodules x 1 + Abscesses x 2 + Draining fistulas x 4.

Secondary outcome

This study has the following secondary outcomes:

- The clinical efficacy of both treatment strategies at the last visit (12 months or the last visit before dropout) using the, 5-point Physician global assessment (PGA), Hidradenitis Suppurativa Clinical Response score (HiSCR), and the amount of flares.
- The changes in quality of life using the EuroQol-5D-5L (EQ-5D-5L) and DLQI at the last visit (12 months or the last visit before dropout)
- The effect of both treatment strategies on serum biomarkers at the last visit (12 months or the last visit before dropout) and cytokine profile in skin biopsies after three months.
- The tolerability and safety of both treatment regimens after 12 months.
- The treatment satisfaction three months after surgery and after 12 months

for both treatment strategies.

- The frequency of metabolic syndrome and pre-diabetes in patients with moderate to severe HS, and the effect of both treatment strategies on parameters of metabolic syndrome and pre-diabetes at the last visit (12 months or the last visit before dropout).

- The (blood) metabolite profile of HS patients, the relation between metabolites or metabolite profiles and HS phenotypes, disease severity and clinical response (at three months), and changes in metabolite profile after three months of treatment.

- Pharmacokinetics of adalimumab; the relation between adalimumab serum trough concentrations and clinical response after three months, the relation between the trough concentration of adalimumab in serum and skin samples after three months, the influence of patient characteristics (including pharmacogenetics) on adalimumab serum trough concentrations at three and at the last visit (12 months or the last visit before dropout), the predictive value of early adalimumab trough concentrations on clinical response at three months, and objectively assessed and self-reported adherence to adalimumab at the last visit (12 months or the last visit before dropout).

- The effect of en bloc surgery the recurrence rate after surgery. The influence of wound size, location, and patient characteristics on the healing time of surgical defects.

Study description

Background summary

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent, inflammatory and debilitating skin disease that usually presents after puberty. HS is characterised by painful, deep-seated, and inflamed boils most commonly in the axillary, inguinal, and anogenital regions. HS is a common disease with an average prevalence of 1% in Europe. It*s association with a variety of concomitant and secondary diseases such as obesity, metabolic syndrome, diabetes, inflammatory bowel disease (e.g. Crohn*s disease), and spondyloarthropathy is currently under investigation. Moreover HS is a highly associated with smoking.

HS has the greatest impact on quality of life (QoL) of patients compared to other dermatological diseases, this is mostly due to the symptoms of pain and foul discharge. It has been reported that patients with severe HS have a work absence rate of on average 34 days per year due to their disease. Some patients even lost their job. Despite this profound impact on patients QoL, HS has suffered from a lack of interest of dermatologists. It was long considered difficult to manage with virtually no effective therapy for the more severe phenotypes of HS. The disease originates form keratinous plugging of the upper part of the hair follicle, resulting in dilatation and subsequent rupturing. The exposure of the dermis to the hair follicles contents leads to a foreign body-like inflammatory response, resulting in abscesses. Aberrant healing leads to sinus tract formation and scarring. The sinus tracts and fistulas are most likely the origin of the recurrent nature of the disease.

In 2015 treatment guidelines have been published in the *European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa*. This guideline suggests that moderate and severe HS should be treated with a combination of antibiotics (e.g. clindamycin plus rifampicin or tetracyclines), vitamin A derivatives (acetretin) and anti-tumour necrosis factor-α (anti-TNF-α) biologicals (e.g. adalimumab). The recent registration of adalimumab for the treatment of HS in Europe (including the Netherlands) is seen as a huge step forward in the management of HS. Not only does it improve HS symptoms it might also impact conditions associated with HS such as metabolic syndrome and insulin resistance and sensitivty. However, the dose of adalimumab needed to maintain a good clinical response in HS patients is twice as high as the dose needed in other diseases such as rheumatoid arthritis (RA) and Crohn*s disease (CD). This results in the accumulation of costs as maintenance treatment will be necessary to supress the disease activity. Even though all of the before mentioned treatments can significantly reduce inflammation and provide symptomatic relief, none resolves the fistula*s and therefore these treatments cannot cure the disease. Although there is no high level evidence, expert opinion recommends a combination of the above treatments with en bloc excision of the affected areas to remove the fistulas. Additionally repeated surgery (en bloc excision) should be preceded by systemic treatment to reduce inflammation

and thereby reduce the area in need of surgery and to reduce the recurrence rate of HS after surgery. However, en bloc excision is associated with a hospital stay of at least two days and a secondary intention healing phase with extensive wound care at home. The surgery and after care may have an impact on patients quality of life, but is likely to recover after the healing is achieved.

Remarkably there are currently no published reports evaluating the effect of the addition of adjuvant surgery to anti-TNF-α therapy in HS. Therefore, this study aims to evaluate the effectiveness of the addition of adjuvant en bloc excision to adalimumab therapy in patients with moderate to severe HS. As adalimumab therapy does not cure the disease, our working hypothesis is that combining this treatment with adjuvant surgery will be more effective.

Study objective

The primary objective of this prospective study is to assess the clinical efficacy of the combination of adalimumab and surgery compared to adalimumab monotherapy after one year of treatment in adult patients with moderate to severe HS at the last visit (12 months or the last visit before dropout) using the International Hidradenitis Suppurativa Severity Score System (delta IHS4)

Study design

This is a randomized, controlled clinical trial in a real life setting with a 12 month follow-up. The inclusion period will span two years. Potentially eligible patients will be informed about the study procedures and will be given ample time to consider their decision. After obtaining informed consent patient will be screened for eligibility. Eligible subjects will be randomised to one of the two study arms, treated and followed for 1 year (V0 up to and including V4). Patients in group A will be treated with adalimumab monotherapy according to normal clinical practice. Patients in group B will receive adalimumab combined with adjuvant en bloc excision of active lesions (under general anesthesia or procedural sedation and analgesia), both according to routine clinical practice. Patients from Group A will be offered the possibility to cross over to Group B when they do not achieve HiSCR after 6 months of treatment. Additionally they will be offered to start infliximab treatment during this period until the last surgery.

Intervention

This study consists of two treatment arms. The intervention consists of a combination of adalimumab and adjuvant surgery. The patients in this group will receive adalimumab treatment and additional surgery to remove HS lesions, with a maximum of two surgical interventions. Surgery will take place at 3 months (V1) and 6 months (V2). The adalimumab treatment will continue continued until

the end of the study.

This treatment strategy will be compared with adalimumab monotherapy. Adalimumab will be administered through subcutaneous injections in weekly dose of 40mg from week 4 up to 12 months (V4), after an initial dose of 160mg at week 0 and a 80mg dose at week 2.

Study burden and risks

Patients will visit the hospital every three months for a duration of 12 months. On all visits blood samples will be collected, in accordance with routine clinical practice. Patients from the intervention group will undergo surgery followed by three hospital visits to evaluate wound healing.

In both groups biopsies will be taken at baseline and three months from lesional skin. A skin biopsy is generally safe, however there is a small risk of bleeding and infection. Patients will complete multiple questionnaires at baseline and every visit thereafter. Filling out these questionnaires at baseline and every even visit thereafter will take approximately 15 minutes, at every even visit approximately 10 minutes. During the adalimumab treatment patients will fill out a weekly diary, this will take approximately 5 minutes per week.

Risks for participating patients consists of the occurrence of treatment related side effects and adverse events, including an increased risk of infection, anaemia, abnormalities in liver parameters, and injection site reactions when treated with adalimumab. Complications arising from surgical intervention include post-operative bleeding, wound infections and local hypoesthesia.The additional risks in this study on top of the aforementioned risks of the standard treatments consits of the risks associated with the biopsies.

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

In order to be eligible to participate in this study, a subject must meet all of the following inclusion criteria:
1. Age >=18 years.
2. Moderate to (very) severe HS defined as a score of >=3 points on the PGA (range 1-5)
3. Indication for adalimumab: uncontrolled disease (HS) under conventional therapy and/or minor surgery.
4. A diagnosis of HS for more than six months prior to baseline.
5. Clearance of HS can reasonably be achieved with two surgical interventions as based on consensus between two dermatosurgeons.
6. Willing and able to undergo general anaesthesia.
7. Able and willing to give written informed consent and to comply with the study requirements.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Contraindication for treatment with adalimumab (sepsis or risk of sepsis, active or latent tuberculosis, serious active local and/or chronic infections, heart failure NYHA class III/IV, severe liver disease, pre-existing HIV, active viral hepatitis, demyelinating disease, or allergy to adalimumab or any other ingredients of HUMIRA®).
2. Previous failure or current use of adalimumab or other anti-TNF-α therapy.

3. Current or recurrent clinically significant skin condition in the HS treatment area other than HS.
4. Presence of other uncontrolled clinically significant major disease.
5. Pregnant and lactating women.
6. Malignancy (except basal cell carcinoma), lymphoproliferative disease or a history of malignancy.
7. Current use of oral antibiotics (a washout period of 14 days is required).
8. Current use of oral corticosteroids (a washout period of 30 days is required).
9. Previous biologic use; a wash-out of at least 5 half-lifes.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-07-2018
Enrollment:	62
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-02-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2021
Application type:	Amendment
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	EUCTR2016-001663-36-NL
ClinicalTrials.gov	NCT03221621
CCMO	NL57498.078.16