Treatment of Hidradenitis Suppurativa Evaluation Study: the THESEUS prospective cohort study

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Equality, diversity and inclusion

Participant representation

Entry criteria for THESEUS were designed to be as inclusive as possible and the baseline demographics of THESEUS participants closely reflects the HS secondary care population in the UK. THESEUS recruited women of childbearing age, with a four to one female to male ratio and an average participant age of 36 years. Regarding smoking and obesity, again, THESEUS participants reflected the overall HS patient population, two-thirds being current or ex-smokers and 86% having a raised body mass index. There was broad representation across socioeconomic groups with half of the THESEUS participants in the most deprived and second-most deprived deprivation quintiles. Just over 20% of THESEUS participants had non-white ethnicity, slightly higher than overall UK population statistics. The 10 recruitment sites chosen for THESEUS were purposively spread across the UK, including sites in southern England, northeast England, northwest England, Scotland and Wales, to ensure that most regions of the UK were involved in the study. Our study centres ranged in size from large tertiary hospitals to smaller district general hospitals, demonstrating that future HS trials can be conducted in a range of settings. During the COVID-19 pandemic, conversion of follow-up to remote appointments if needed ensured that the participants' access to their study team was not interrupted. Remote appointments also helped participants with mobility problems and transport difficulties. Our study results reveal that meetings and other patient meetings were also held online, again improving access for those with physical disabilities. On discussion with THESEUS patient research partners, we chose a hybrid model for the end-of-study workshop. In-person attendance was felt to maximise workshop contributions; however, some of our patient participants preferred to join online due to work or child-care commitments and because of physical disability. The solution was to select a venue with good videoconferencing facilities and, for the small group discussions, there were two in-person groups and one online, each with a facilitator. The potential financial impact of attending the workshop was mitigated by compensating patient attendees at the Involving People daily rate. Male patient representation was specifically sought for the workshop in the context that while HS is a condition in the UK predominantly affecting females, males are also affected as a minority. Only one person with HS featured in the deroofing video so there was not the chance to include a wide range of patient demographics in this aspect of the study. Ensuring that materials and videos for future studies encompass a full range of diversity will be an important element to consider.

Reflections on the research team and wider involvement

The THESEUS research team had substantial patient and public involvement (PPI) in study planning, funding application, study delivery and organising the end-of-study workshop. We were fortunate that one of our research partners is an expert in equality, diversity and inclusion (EDI) and they guided THESEUS regarding EDI considerations. We were able to involve a HS patient carer in the study planning process to ensure representation from this stakeholder group as well. Participant recruitment involved junior doctors, whenever possible, to help provide clinical trial training to the next generation of researchers.

Final approval was provided by Dr J Ingram.

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Scientific summary

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Scientific summary

Background

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterised by recurrent inflammatory nodules, abscesses and skin tunnels in flexural sites including the axilla and groin. Flares are very painful, may produce pus and scarring and have a large impact on quality of life. Prevalence is about 1% of the UK population and HS particularly affects young adult women, detrimentally affecting relationships and employment.

Multidisciplinary team (MDT) management is recommended, integrating drug treatments that reduce HS inflammation and surgery to manage scarring. A consensus process conducted by the Hidradenitis SuppuraTiva cORe outcomes set International Collaboration (HiSTORIC) defined outcome domains to measure in HS trials and validation of outcome measure instruments (OMIs) to assess each domain is underway.

The Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS) addressed several questions prioritised in the James Lind Alliance Priority Setting Partnership (PSP) for HS, including what is the most effective and safe group of oral treatments in treating HS (ranked number one priority), what is the impact of HS and the treatments on people with HS (ranked third) and what is the best surgical procedure to perform in treating HS (ranked sixth).

Deroofing is a surgical procedure usually performed under local anaesthetic allowing targeted removal of HS subcutaneous skin tunnels by blunt skin probing followed by removal of the tunnel roof and secondary intention healing of the base. It is routinely performed in several countries but not the UK. Laser treatment targeting the hair follicle is another well-recognised intervention for HS not currently used in the UK.

The Treatment of Hidradenitis Suppurativa Evaluation Study was designed as a prospective cohort study to introduce deroofing and laser treatment for HS in the UK and to understand how conventional surgery and oral antibiotics are currently used.

Objectives

1. To understand current HS patient pathways and what influences patients' and clinicians' treatment choices to inform the design of future randomised controlled trials (RCTs).
2. To determine the feasibility of recruiting individuals with HS into clinical trials.
3. To fully characterise the THESEUS drug and procedural interventions.
4. To test the feasibility and responsiveness of OMIs for HS trials.
5. To explore consensus-agreed recommendations for future RCT study designs.

Methods

Study design

A multicentre prospective observational cohort study, including five treatment options, with nested process evaluation, including participant and clinician interviews, and an end-of-study consensus workshop.

Recruitment and follow-up

Participants were recruited from 10 hospitals across the UK. Six sites were dermatology-led, two were plastic surgery-led and two had HS MDTs. Initial treatment was for 6 months, during which participants stayed on their chosen intervention, after which intervention switching was permitted, with an additional 6 months of follow-up. Reviews occurred every 3 months after recruitment and a study amendment allowed remote follow-up due to the COVID-19 pandemic. Sites were required to offer at least four of the five THESEUS interventions.

Eligibility criteria

Adults of at least 18 years with active HS not adequately controlled by current treatment were eligible for the study. Disease definition was a lifetime history of at least five flexural skin boils or two flexural skin boils in past 6 months, confirmed by a recruiting clinician with experience of HS care. Provided at least one of the study interventions was appropriate for the participant, any level of disease severity was acceptable.

Exclusion criteria were being unable or unwilling to give informed consent, pregnancy or breasteeding, and being unable to complete outcome questionnaires in English. Participants could continue their current treatment on study entry.

Interventions

1. oral doxycycline 200 mg once daily;
2. oral clindamycin and rifampicin both 300 mg twice daily for 10 weeks initially;
3. laser treatment targeting the hair follicle: neodymium-doped yttrium aluminium garnet (Nd-YAG) or alexandrite;
4. deroofing;
5. conventional surgery, procedure and closure method as per site's usual practice.

Participants could choose their intervention subject to availability on discussion with their clinician, who advised on the suitability of the interventions, the shared decision-making process mirroring usual clinical practice. Participant choice was supported by a decision grid (https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/theseus) providing a description and head-to-head comparison of THESEUS interventions.

Outcomes

Primary outcome

Proportion of participants eligible, and hypothetically willing, to use the interventions.

Secondary outcomes

- proportion of participants choosing each study intervention, with reasons;
- proportion of participants switching treatments, with reasons;
- treatment fidelity;
- loss to follow-up over 12 months;
- efficacy outcome estimates after 6 months' follow-up, informing OMI responsiveness.

Safety

As an observational study, investigators followed their usual process for managing adverse events, for example yellow card reporting, and adverse event data were collected at scheduled study visits.

Daily pain score

For 12 weeks after the intervention was commenced, participants were sent a daily text message to record the magnitude of their current pain due to HS from 0 to 10 using the pain numerical rating scale (NRS).

Sample size

The target sample size was 150 participants, permitting estimation of the proportion of participants hypothetically willing and eligible to be randomised in a clinical study within a 95% confidence interval (CI) of ±7%. Preliminary survey work ascertained that the sample size should ensure at least 20 participants were recruited for each intervention, sufficient to explore delivery in an IDEAL 2b evaluation.

Statistical methods

Study participation (screened, eligible, recruited, withdrawals) and completeness of follow-up was illustrated by a Consolidated Standards of Reporting Trials (CONSORT) flow diagram. For the primary outcome, willingness and eligibility data were combined for each intervention. THESESUS was not powered to test hypotheses and most analyses were descriptive. Continuous data were reported as means and standard deviations or medians and interquartile ranges, as appropriate, and categorical data reported as frequencies and proportions. Analysis and results were based on the participants' final treatment selection.

Treatment fidelity was measured by self-reported concordance at each follow-up. Effect over time was estimated for efficacy outcomes for each intervention with 95% CIs. The pattern of missingness of daily pain scores during 12-weeks was examined for levels of completion.

Patient and public involvement

Patient and public involvement (PPI) representatives were involved in THESEUS from the outset, two leaders of the HS Trust patient advocacy organisation being funding co-applicants and a further two PPI representatives joined the study management group and one joined the study steering group. The creation of a decision grid was requested by THESEUS PPI members and they reviewed all patient-facing study documentation. Specific PPI representative feedback led to chlorhexidine solution being removed as a cotreatment from the doxycycline intervention arm to avoid misconceptions that HS is linked to poor personal hygiene. PPI representatives directed the timing of the daily text messages, requested a patient version of a deroofing information video and advised on flexible remote follow-up to mitigate for COVID-19 pandemic disruption.

Following discussion with THESEUS PPI representatives, it was decided to host a combined results reveal meeting for trial participants, clinicians and researchers. THESEUS patient research partners guided logistical arrangements for the end-of-study workshop and led two participant meetings beforehand.

Results

Between February 2020 and July 2021, 151 participants were recruited. Recruitment was affected by the COVID-19 pandemic and there were two substantial pauses which mirrored two waves of the pandemic in the UK. Outside these periods, a recruitment rate of 15–20 participants per month was achieved. Follow-up rates were 89% and 83% after 3 and 6 months, respectively, decreasing to 42% at 12 months, in part because pandemic recruitment delays prevented all participants from reaching their final study review.

Baseline demographics of THESEUS participants were in keeping with secondary care HS patients, with an average age of 36 years, 81% female, two-thirds current or ex-smokers and 86% with a raised body mass index (BMI). There was a slightly higher proportion of non-white participants than the UK average, with 20% being black, Asian or Caribbean. Baseline disease severity again reflects the HS secondary care population, two-thirds having moderate disease, 19% severe disease and 13% mild disease.

Regarding THESEUS's primary outcome, laser treatment was the intervention with the highest proportion (69%) of participants who were eligible and hypothetically willing to receive treatment, followed by deroofing (58%), conventional surgery (54%), oral clindamycin and rifampicin (44%), and finally doxycycline (37%). Considering participant willingness in isolation, laser was ranked the first choice by the greatest proportion (41%) of participants. Final intervention choice mirrored the primary outcome, except the proportion choosing laser treatment was lower because it was offered by only 6 of the 10 recruiting sites. The cohort study and nested qualitative study results demonstrated participant willingness to receive treatment and final intervention choice were strongly influenced by clinicians. 'My doctor recommended it' was the most common reason (59%) given by participants for their final choice.

Fidelity to oral doxycycline was only 52% after 3 months due to lack of effectiveness, participant preference and adverse effects. Continuation of clindamycin and rifampicin after 3 months was affected by the standard course being 10 weeks initially, reflected by only 30% still receiving treatment after 12 weeks. Delays receiving procedural interventions were common, with only 43% and 26% of participants commencing laser therapy and deroofing, respectively, after 3 months. Treatment switching was uncommon, with only five participants switching from laser and nine switching from deroofing. There were no serious adverse events reported.

Those receiving doxycycline had modest improvements after 3 months in median International Hidradenitis Suppurativa Severity Score System (IHS4) score from 7 to 6, Dermatology Life Quality Index (DLQI) score from 6 to 3.5 points, Hidradenitis Suppurativa Quality of Life score (HiSQOL) score from 26.5 to 11.5 and pain NRS from 2 to 1. Small effect sizes are in part due to relatively low baseline disease severity in the doxycycline group. Corresponding score changes for clindamycin and rifampicin at 3 months were decreases in IHS4 score from 11 to 5 points, DLQI score from 14 to 10.5 points, HiSQOL score from 34 to 23 and pain NRS from 4 to 2. The variable timing of procedural interventions limited interpretation of efficacy data for these interventions with follow-up reviews fixed in time after recruitment.

Daily pain score text messages were initiated in 110 participants and 100 returned at least one score. Daily responses reduced over time and the median duration of concordance was 36 days. A higher level of completion occurred in the first 14 and 28 days.

Characterisation of deroofing and laser

Deroofing was a popular intervention with both clinicians and participants, reflected by more than 1 million views of the THESEUS study video (https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/theseus). Deroofing proved straightforward for sites to adopt, both those led by plastic surgery and dermatology departments. The instrument used for incision varied, with needle tip diathermy used more often than loop tip diathermy. However, identification of skin tunnels by blunt probing and removal of the tunnel roof with secondary intention healing were highly conserved.

Unintended variation was encountered in the laser group, one-third of treatments being intense pulsed light (IPL) rather than laser treatment. The effect of the two interventions is similar because both target the hair follicle and there is evidence supporting IPL for HS. The THESEUS laser protocol specified double pulse treatment for HS lesions and single pulses for neighbouring unaffected skin; however, considerable variation was observed.

It was not possible to characterise conventional surgery due to the low number of participants in this group, in part reflecting preference for deroofing.

Process evaluation

The qualitative studies aimed to understand participants' and clinicians' perspectives on treatment choices and to identify recruitment barriers and facilitators for future trials. Semistructured participant interviews were conducted by telephone using a topic guide and subsequent thematic analysis. Purposive sampling ensured diversity of participants across the five interventions. Interviews demonstrated that intervention choice was influenced by 'push' factors such as lack of efficacy and adverse effects if an intervention had been received previously and 'pull' factors such as the novelty of laser treatment and deroofing. Participants supported flexibility in remote compared with in-person follow-up and highlighted the need to minimise questionnaire burden.

Consensus workshop

In June 2022, a 1-day consensus workshop occurred, informed by THESEUS results. Nineteen individuals attended in person, including six people living with HS. Fourteen individuals attended remotely via videoconferencing. The workshop was preceded by two meetings for patients and a pre-workshop survey asked for initial voting on interventions to investigate in future HS RCTs. Early intervention to prevent HS scarring was agreed upon as a general principle. The workshop prioritised combined laser and medical therapy, which could be compared with laser or medical therapy, potentially in a multiarm study. Combination therapy with biologic treatments such as adalimumab was considered and deroofing was also prioritised, either for chronic lesions or for acute flares.

Conclusions

Implications for health care

Offering medical and non-medical interventions, THESEUS encouraged an MDT approach to optimise HS care. Training and equipment provided by THESEUS established deroofing as a surgical option, bringing the UK in line with other countries. Deroofing is a tissue-sparing treatment for tunnels and can also be adapted for acute flares, the latter being ranked second highest priority in the HS PSP. A need for deroofing is demonstrated by 1 million views of the THESEUS deroofing video. While laser and light hair removal treatment was already available in the UK, it was rarely used for HS therapy and THESEUS showed that it can be provided for HS within existing infrastructure.

Use of HiSTORIC-developed OMIs for HS familiarised 10 centres with well-validated tools to monitor patient progress. Several OMIs are suitable for routine clinical care; for example, HiSQOL can be completed in the waiting area before appointments.

Implications for research

The Treatment of Hidradenitis Suppurativa Evaluation Study was designed to underpin future HS RCTs. The 10 THESEUS sites are well-placed to be recruiting centres in future trials, which, from the THESEUS workshop, are likely to involve laser or deroofing. Whether to allow IPL within a laser and light hair removal treatment intervention in a future RCT will depend on availability of Nd-YAG and alexandrite lasers and whether the study is more explanatory or pragmatic in design.

The nested qualitative study provided multiple insights for future trials. A RCT with an active comparator will need to ensure equipoise for participants and clinicians and provide equivalent information, for example study videos, for each intervention. Flexibility should be offered where possible

for in-person or remote appointments. OMIs should be minimised and carefully explained. Collection of daily pain scores remotely is feasible, but it should be restricted to short periods.

Delivering the planned recruitment of 150 THESEUS participants despite the COVID-19 pandemic demonstrates that future RCTs for HS in the UK are feasible and will be well-supported by patients and health-care professionals (HCPs).

Trial registration

This trial is registered as ISRCTN69985145.

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This report

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