General introduction and aims of this thesis

Parts of the introduction are based on:

Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model

Frontiers in Immunology – accepted for publication

Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimisation – systematic review and recommendations from the HS ALLIANCE working group

J Eur Acad Dermatol Venereol – in press

Surgical approaches to hidradenitis suppurativa management

Dermatologic Surgery, New York: McGraw Hill, 2018

BACKGROUND

Hidradenitis suppurativa (HS), also known as acne in versa, is a common chronic, recurrent, inflammatory follicular occlusive disease. Estimated prevalence of HS in Europe and North America range from <1% to 4%.[1,2] The disease usually presents after puberty with painful, deep-seated inflamed lesions, predominantly at inverse body sites carrying terminal hairs such as the axillae, inguinal and anogenital regions.[3] Atypical areas including the nape, retro-auricular areas and the back can also be affected.[4]

Key symptoms of HS include chronic pain, discomfort, and a purulent, malodorous discharge.[5] The major factors influencing the patients well-being are disease severity, the number of flares or affected skin areas, and the lesion location.[6] The physical and psychological consequences of HS can profoundly reduce several aspects of patient's quality of life. This is demonstrated by the affected scores of questionnaires for general health (EQ-5D and SF-36), dermatologic-specific quality of life (DLQI and Skindex), and sexual health.[6-8] The impact of HS on general health (EQ-5D) can be compared with cerebrovascular stroke, diabetes mellitus or severe chronic obstructive pulmonary disease.[6] In addition, rates of depression and anxiety among HS patients are significantly higher than in healthy controls.[9] Collectively, this might explain the significantly increased completed suicide risk is in patients with HS.[10]

The pathogenesis of HS is not fully understood. Several factors contribute to the onset and maintenance of the disease. Genetic predisposition is a well-known endogenous factor, as demonstrated by a positive family history being reported by 30-40% of the patients.[3] Exogenous risk factors include a positive smoking status and obesity.[11] In addition, HS is linked to a number of comorbid diseases. Data suggest that HS is most convincingly associated with the metabolic syndrome including the report of higher rates of diabetes mellitus, which may explain the significantly increased risk of adverse cardiovascular events.[12-14] More recently, several immune mediated inflammatory diseases have been linked to HS, notably inflammatory bowel disease and spondyloarthropathy.[12,15] HS can also occur in the context of auto-inflammatory syndromes such as pyoderma gangrenosum, acne and suppurative hidradenitis (PASH).[16]

PATHOPHYSIOLOGY

Current evidence highlights a complex multifactorial pathogenesis.[17] A key triggering factor is the occlusion of the hair follicle, caused by keratosis and hyperplasia of the follicular epithelium leading to cyst development.[18,19] Subsequently, the cyst will rupture, causing a fierce immune response and inflammation that, depending on the

severity, may progress to abscess and sinus tract development and scarring.[18,19] The name of the disease implies that sweating and bacterial infection are a fundamental part of the disease process. This is misleading and now considered a misnomer as no evidence has been found that HS is triggered by events in the apocrine or eccrine glands. Recent findings on the pathogenesis of HS and its syndromic forms are largely derived from four main lines of investigation: genetics, inflammatory markers, bacteriology including the microbiome, and physiological and environmental factors.

Genetics

Mutations in γ-secretase genes whose gene products act on many substrates including Notch,[20] suggest that Notch or other substrates of γ-secretase and/or phosphoinositide 3-kinase (PI3K) may play a role in the pathogenesis of HS.[21] However, the functional significance of γ-secretase remains elusive. Interestingly, γ-secretase knock-out mice are characterised by a phenotype of multiple cutaneous cysts, a key feature of HS.[22] However, these mice did not exhibit skin inflammation,[22] and nicastrin (*NCSTN)* mutations in HS did not enhance cytokine production in LPS-stimulated peripheral blood mononuclear cells.[23]

There is also evidence of mutations to the proline-serine-threonine phosphatase interacting protein 1 *(PSTPIP1)* gene in cases of PASH and pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PAPASH) syndromes.[24,25] A mutation in the *PSTPIP1* gene resulted in a case of pyoderma gangrenosum (PG), acne and ulcerative colitis (PAC), in which the associated elevated interleukin (IL)-1β levels were responsive to the IL-1 receptor antagonist anakinra.[26] PSTPIP1 is a cytoskeleton-associated adaptor protein, highly expressed in hemopoietic cells.[26] The PSTPIP1 protein manifests its immunomodulatory effects through downregulation of CD2 adhesion, regulation of c-Abl tyrosine kinase activity, and interaction with other immunity-related proteins including the Wiskott–Aldrich syndrome protein (WASp)[27], and pyrin and the familial Mediterranean fever (FMF) protein.[26] Furthermore, a genetic analysis of auto-inflammation in PG and the syndromic form PASH identified mutations in a range of auto-inflammatory genes (*MEFV*, *NLRP3*, *NLRP12*, *NOD2*, *LPIN2* and *PSTPIP1*), suggesting the involvement of inflammatory pathways such as NLRP inflammasomes, cystolic pattern recognition sensors, the innate immune system, and IL-1β signalling (*PSTPIP1*).[16]

The majority of HS cases appear to be non-familial, suggesting the existence of separate subsets and the need for stratification of patients diagnosed with HS.[28] In a study of 139 unrelated patients with non-familial HS, single nucleotide polymorphisms of the *IL-12Rb1* gene coding for the IL-12Rb1 receptor subunit did not genetically predispose to HS.[29] However, their carriage was directly associated with the phenotype of HS, indicating the importance of the IL-12/23 pathway for the pathogenesis of

HS. Findings from a case-control study of two independent and genetically diverse cohorts of patients with non-familial HS from Greece (n = 163) and Germany (n = 98) suggested that the copy number of the β-defensin gene cluster (DEFB) confers susceptibility for HS and modulates the disease phenotype.[30]

Inflammatory markers

Clear evidence suggests the involvement of pro-inflammatory cytokines in the immune dysregulation of HS, with elevated levels of tumour necrosis factor (TNF)-α, IL-1ß, IL-6, IL-17 and interferon (IFN)-γ observed in HS lesions.[17,31,32] The immune dysregulation is initiated by caspase-1 activity in the inflammasome which lead to the secretion of the pleiotropic cytokine IL-1β, thereby stimulating the infiltration of inflammatory cells and the induction of chemokines.[33] As a result, a number of inflammatory markers, most of them related to the IL-17 pathway, have been found elevated in HS skin and serum on the mRNA and/or protein level.

Alterations in the skin have recently been reported for IL-1β[16], CXCL-8/IL-8[16,34], IL-17/IL-17A[16], IL-23p40[35], IL-32[36], and IL-36/IL-36α/IL-36β/IL-36γ[34,37]. Data also indicate the involvement of T helper (Th) cells, which accumulate in HS lesions, in the pathogenesis of HS.[32,38] In addition, studies have shown that antimicrobial peptides (AMPs) are increased in HS lesions compared with the normal skin of HS patients.[39] Keratinocytes isolated from HS patients exhibited a pro-inflammatory profile and a dysregulated production of AMPs such as HBD-2, psoriasin (S100A7) and calgranulin B (S100A8), indicating that the skin immune system is already activated in the steady state.[40]

Alterations in the serum have recently been reported for IL-1β[41], IL-6[41], CXCL-8/IL-8[41], IL-10[41], IL-12p70[41] and IL-17/IL-17A[41,42]. In addition, TNF-α, S100A8, and S100A9 have been found to be upregulated in the circulation of HS patients.[43,44] Systemic inflammation is also demonstrated by elevated levels of c-reactive protein (CRP), erythrocyte sedimentation rate, neutrophils, and monocytes.[41,45] A significant association between CRP levels and neutrophil count with HS disease severity has been reported.[46] Lastly, the use of TNF-α inhibitors such as adalimumab and infliximab have been associated with improvements in immune dysregulation in HS, which supports the importance of (local) molecular drivers in the pathogenesis of HS.[3,47,48]

Bacteriology and the microbiome

A number of studies investigated bacterial cultures from HS lesions and generated evidence for the involvement of microbes in the disease pathogenesis. A histological study of 42 patients with chronic HS identified bacterial aggregates (biofilms) in 67% of chronic lesional samples and in 75% of perilesional samples.[49] The same author group conducted a case-control study of punch biopsy specimens and demonstrated

that the microbiome in patients with HS differs significantly from that in healthy controls in both lesional and non-lesional skin.[50] A microbial analysis of lesional versus unaffected skin from 65 patients with HS identified anaerobic microbes in 83% lesions versus 53% control samples, and the microbiome varied with disease severity.[51] These bacteria were associated with low pathogenicity. An extensive prospective microbiological study identified two opportunistic bacterial pathogens associated with HS lesions (*S.lugdunensis* and anaerobic actinomycetes).[52] These pathogens can cause abscesses and severe infections. A cross-sectional study of 50 patients reported that bacterial colonisation was correlated with severity and localisation of HS lesions.[53] Over two thirds (68.8%) of patients with both aerobic and anaerobic bacteria had the most severe grade of HS (Hurley stage III).

Physiological and environmental factors

Recent literature supports the involvement of previously suggested physiological and environmental risk factors, such as smoking and obesity, in HS.[46,54,55] A postal follow-up survey study (N = 212) found the chance of remission from HS may be improved in non-smokers versus smokers, and in non-obese (body mass index [BMI] <30) versus obese patients.[54] In contrast, a retrospective study of inflammatory serum markers in HS patients found no association between smoking status and HS severity, but smoking was associated with increased neutrophil counts.[46] This study did find an association between increased BMI and HS severity whereas there was no correlation between BMI and neutrophil counts.

Related to obesity, an analysis of 14 obese patients with HS described the role of mechanical stress (for example on the abdomen at the level of the waistband) in promoting a 'Koebner-like phenomenon' in HS.[55] The development of lesions at sites of traumatised but previously uninvolved skin highlights the importance of localised environmental factors in HS development. A hospital-based cross-sectional study conducted in the Netherlands reported a significantly higher average BMI in 106 patients with HS than in 212 general dermatological patients.[56] Among those patients identified as obese, bodyweight distribution was more peripheral in patients with HS than those without, consistent with enhanced friction due to overlapping skin folds.

The influence of hormones has been suspected in women with HS for more than 60 years yet has not been proven.[57] Kromann and colleagues reported no clear effect of pregnancy or menopause on HS symptoms.[54] However, a substantial subset of women did experience HS-related alterations, with deterioration of HS around menses and amelioration of symptoms during pregnancy reported in 43% (n = 80) and 30% (n = 29) of the respondents, respectively.[58] This study found a significant correlation between perimenstrual deterioration of HS symptoms and amelioration during pregnancy.

Integrated viewpoint on HS pathogenesis 'sequence of events'

On the basis of the latest evidence, we are able to propose a three-stage sequence of events that contribute to the pathogenesis of HS. This integrated viewpoint is illustrated schematically in Figure 1.

The first event is follicular occlusion with subsequent dilation. This may be driven by endogenous factors in individuals harbouring a genetic predisposition for an enhanced risk of infundibular keratinisation and cyst formation and/or follicular fragility. Exogenous factors such as smoking, mechanical friction and metabolic changes such as obesity – which is associated with pseudoacanthosis – also contribute to occlusion of the follicular isthmus. Furthermore, occlusion of the hair follicle may lead to a dysregulation of the homeostatic keratinocyte symbiosis and microbial dysbiosis, making the skin prone to a Th1/Th17-driven inflammatory disease.

The second event is rupture of the dilated follicle. The scattering of follicle content in the dermis including keratin fibres, commensal flora or pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) triggers an acute and severe immune response. The anatomical location, i.e. the inverse body areas, and enhanced mechanical friction at these predilection sites facilitates the inward rupture and extension of inflammation. We argue that the release of the follicular debris into the dermis results in simultaneous activation of multiple inflammatory pathways, particularly Th17/IL-23, the NLRP inflammasomes and innate receptors (toll-like receptors, TLRs such as TLR2). This is accompanied by histological alterations with a diverse cell infiltrate characterised by the mixed participation of monocytes, neutrophils, eosinophils, multinucleated giant cells, B-cells, plasma cells, T-cells, and natural killer cells, leading to an erythematous nodule or fluctuating abscess.

The third event is chronic inflammation with sinus tract or tunnel formation. Following follicular rupture, sequestered proliferating Ki-67+ epithelial strands promote continuous activation of the immune system. The presence of epithelial strands in the dermis, in addition to an imbalance in matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), and increased activity of fibrotic factors such as transforming growth factor (TGF)-ß 1-2-3, may lead to scarring and the development of sinuses/tunnels or fistulae, a hallmark of chronic HS. These (partly) epithelialised intracutaneous cavities provide an excellent habitat for biofilm-producing bacteria, which are able to continuously trigger inflammation with associated purulent drainage. Furthermore, we hypothesise that circulating pro-inflammatory cytokines and chemokines from chronic lesions may activate the immune system of the hair follicle in distant predilection sites.

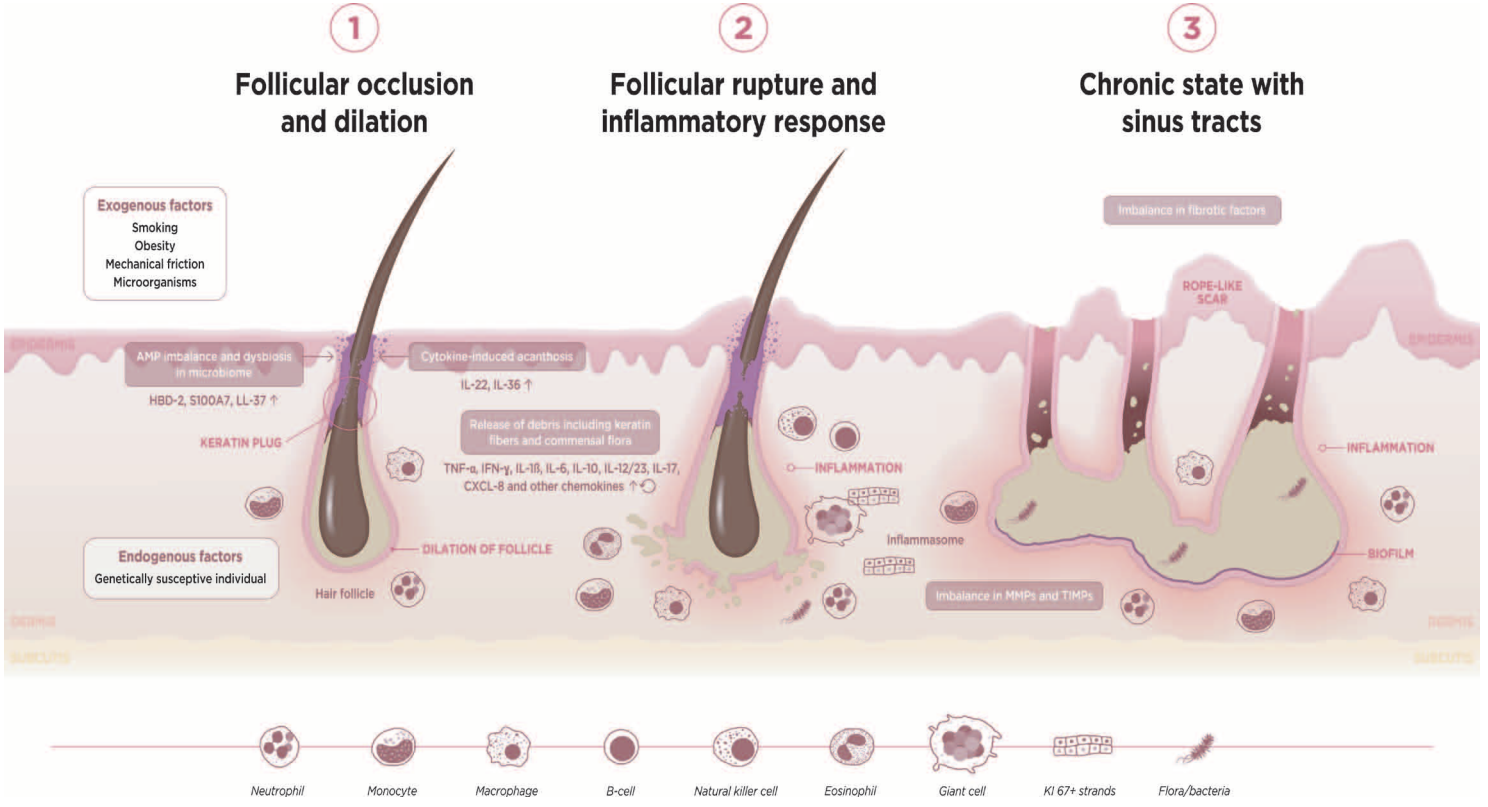

Figure 1. Schematic diagram to illustrate postulated sequence of events underlying HS pathophysiology. Adapted from Saunte and Jemec, 2017. AMP: antimicrobial peptide. HBD: human ß-defensin. IFN: interferon. IL, interleukin. MMP: matrix metalloproteinase. TIMP: tissue inhibitor of metalloproteinase. TNF: tumour necrosis factor.

TREATMENT

To date, there is no long-term cure for HS. In general, the main treatment goal is to improve patients' quality of life. This can be achieved by reducing the inflammation-related pain and purulent discharge, limiting the incidence and duration of flares, and removing chronic lesions using surgical techniques. As there are limited effective treatment options, there remains a large unmet medical need in this area. To date, only eight randomised controlled trials (RCTs) have investigated the efficacy of anti-inflammatory agents. The highest-level evidence available addresses the use of biologic therapies, especially adalimumab (anti-TNF-α), and topical and systemic antibiotics. The majority of the remaining evidence to guide management decisions is based on case reports, small cohort studies and expert opinion.

Anti-inflammatory antibiotics

The literature available on the use of antibiotics in HS is limited and largely restricted to retrospective studies. For Hurley stage I, topical clindamycin 1% is a possible therapy, especially in the absence of abscesses.[59,60] If there are several lesions and frequent exacerbations, the therapeutic group of systemic tetracyclines may be considered.[60] In Hurley stage II/III patients who have several active lesions, systemic clindamycin and rifampicin (dosage: 300 mg twice daily) should be administered.[61-64] A triple regimen of rifampicin (10 mg/kg once daily), moxifloxacin (400 mg once daily) and metronidazole (500 mg thrice daily) administered for up to 12 weeks, with metronidazole discontinuation after 6 weeks, may be an alternative option.[65] To limit resistance, only one antibiotic of the same class should be used for a maximum of 12 weeks. The S1 European and HS ALLIANCE guidelines recommend that antibiotics should be reintroduced in case of recurrence under the requirement that they were effective at the last time of use.[3] Of note, in HS, traditional microbiological sampling is not necessary as there is no evidence for infection as a causal factor. Moreover, antibiotics are prescribed in HS for their anti-inflammatory properties, rather than for their antibacterial action.

Biologics

Biologics targeting TNF-α have been most widely investigated in HS and adalimumab is the only registered drug for HS. Adalimumab should be considered as a first-choice biologic agent in moderate-to-severe HS after failure of conventional treatments.[66-68] Infliximab has also been shown to be effective and should be considered as a second-line biologic for moderate-to-severe HS.[69] Targeting IL-1 gave ambiguous clinical outcomes and is considered as third-line option. On the one hand anakinra proved to be efficacious in moderate-to-severe HS in a RCT, but on the other hand cases of

failure to anakinra therapy have been reported.[70-72] Ustekinumab (anti-IL-12/23p40) is potentially effective for the treatment of moderate-to-severe HS.[73] Secukinumab (anti-IL-17A) has demonstrated clinical improvement of HS in single cases,[74,75] and the results of two RCTs (ClinicalTrials.gov Identifier: NCT02421172, NCT03248531) investigating IL-17 antagonists are being awaited.

Surgical treatment

Surgery is indicated throughout all stages of the disease.[76] The presence of inflammation and suppuration determines the need for anti-inflammatory treatment before surgery, e.g. oral antibiotics or biologics. The required surgical intervention is chosen based on the nature of the symptoms, the type of lesions, the presence of sinus tracts, and the size of the area. The evidence for surgical therapies in HS is based on case series and cohort studies with differing methodologies and outcome definitions, impeding the mutual comparison of studies that investigate surgical techniques in HS.

To ensure the best patient outcomes, surgeons should select the appropriate surgical technique based upon operator experience and the individual needs of the patient. A small excision or deroofing can be used for recurrent nodules at fixed locations or sinus tracts in limited areas.[77,78] Wide excision of an entire affected area (body surface are >1%), with removal of (non-)inflamed sinuses, nodules and scar tissue, is indicated for patients suffering Hurley III stage disease.[79-81] Special attention should be paid to patients with perianal and/or perineal HS due to the possible existence of fistulas.[82,83] In addition to electrosurgical (or cold steel techniques), ablative CO_2 laser treatment is an effective alternative method.[84,85]

Secondary intention healing is the preferred management after excisions in HS. Theoretically, secondary intention healing may reduce the rate of recurrence by allowing the remaining aberrant keratinocytes or residual keratin fibres to escape from the wound. Trapping these remnant foci of diseased tissue by primary closure or reintroduction of hair follicles in a predilection site by flap reconstruction may induce recurrence in the operated area. However, to date there is no literature available to support this hypothesis.

Other therapies

Various other treatments have been investigated in HS, but their applicability to widespread practice and outcomes is currently unknown.[86] Further research is warranted for these therapies. Systemic acitretin may be considered as a third-line therapy for patients with mild-to-moderate HS.[87-90] The combination of oral zinc gluconate 30 mg thrice daily and topical triclosan 2% twice daily is a treatment option in Hurley I-II patients.[91] Systemic dapsone 50-200 mg daily induced improvement of HS in 38% (9/24) of treated patients.[92] Metformin at a maximum dose of 500 mg thrice

daily showed clinical amelioration of HS,[93] and could therefore be an adjuvant treatment in obese HS patients at risk for developing diabetes mellitus or the metabolic syndrome. Low-dose systemic corticosteroids (10 mg prednisolone equivalent per day) may be an effective adjunct in recalcitrant HS.[94] Lastly, laser- and light-based treatments have shown promising results for patients with HS in different disease stages.[86] These treatments include the use of intense pulsed light or Nd:YAG laser and external or intralesional photodynamic therapy.

Acute management of flares

Flares of disease, characterised by the acute onset of painful nodules or abscesses, are a hallmark of HS. Adequate management of flares is an essential part of the treatment strategy because acute lesions can be extremely painful and interfere heavily with daily life. Self-treatment of acute lesions can be performed by the application of resorcinol 15% cream thrice daily.[95] Both the keratolytic and mild antiseptic properties of this topical agent has the potential to reduce levels of pain and achieve early clinical resolution of a treated boil. In a clinical setting, inflammatory nodules often benefit from intralesional corticosteroids by inhibiting the synthesis of pro-inflammatory cytokines,[96] whereas abscesses require incision and drainage to rapidly relieve symptoms of pain and pressure.[97-99] Of note, incision and drainage should not be considered as a sole treatment because recurrence is almost inevitable.

AIMS OF THIS THESIS

In HS, rapidly evolving understanding of pathogenic mechanisms and clinical perspectives are needed to improve disease awareness, disease management, and ultimately improve patient outcomes. Because multiple facets of HS are not yet known, the outline of this thesis is not limited to only one aspect of the disease. Using a translational approach, we focused on clinical features and (immuno)pathogenic mechanisms as a rationale for the development of novel treatment strategies.

In our clinical experience a substantial proportion of patients reports itch, also known as pruritus. Therefore, the aim of **Chapter 2** was to investigate the significance of HS-related pruritus by determining the prevalence of pruritus, and exploring its impact on daily activities in a cohort of HS patients. In addition, a selection of serological and histological markers of pruritus were evaluated in a subpopulation.

Extensive inflammation is a clinical hallmark of HS and identification of important inflammatory markers in the pathogenesis of HS may help both therapeutic stratifica-

tion. Consequently, in **Chapter 3** we investigated the cytokine and chemokine profile in the plasma and lesional skin of HS patients.

Biologics targeting inflammatory mediators are now widely used for the treatment of HS in daily practice, but their clinical efficacy shows great inter-patient variability. For that reason, the aim of **Chapter 4** was to determine the anti-inflammatory potency of currently available biologics for the treatment of HS in an *ex vivo* skin model using lesional HS biopsies.

High-quality evidence on HS treatment is limited, highlighting a significant unmet need for novel effective anti-inflammatory therapies. The aim of **Chapter 5** was to investigate the efficacy of apremilast in patients with moderate HS using a randomised placebo-controlled trial design. In **Chapter 5.1** the clinical efficacy, and short-term safety and tolerability of apremilast were evaluated. In **Chapter 5.2,** in a mode of action study, we analysed the change in expression of inflammatory markers in lesional skin of patients receiving apremilast compared with placebo.

As follicular occlusion is the primary event in the HS pathophysiology, we hypothesised that reducing the number of hair follicles would ameliorate the disease course. The aim of **Chapter 6** was to evaluate two non-invasive techniques that (primarily) target the hair follicle in patients with mild HS. In **Chapter 6.1** we assessed the effect of hair removal using a long-pulsed 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) laser. Lastly, in **Chapter 6.2**, the efficacy and safety of microwave ablation for mild axillary HS was evaluated in a randomised intrapatient-controlled trial.

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