Hidradenitis suppurativa: impact of environmental factors and new treatment options

Bouwman, Klasiena

DOI:
10.33612/diss.790615655

Chapter 8

General discussion and future perspectives

K. Bouwman

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Hidradenitis suppurativa (HS) is a chronic and heterogeneous inflammatory skin condition. It primarily develops in intertriginous areas, including the axilla, groin, and perineal regions. HS normally presents with recurrent painful nodules and/or abscesses, and in more advanced disease sinus tracks can develop.[1] Despite the continuing research and rising publication numbers in the last decades, HS remains often refractory to treatment and the exact pathogenesis including contributing environmental factors seems complex.[1] This thesis contributes to the expansion of the knowledge of several aspects of HS, as it provides insights into the prevalence and concomitant comorbidities of HS, the role of lifestyle, and various treatment modalities.

Epidemiology and comorbidities

The true prevalence of HS is still unknown. The broadly accepted prevalence of ~1% can be questioned as significant differences in prevalence and incidence data are published with prevalence ranges worldwide. Studies investigating the prevalence of HS roughly used one of three approaches based on different methodologies including (I) registry-based studies; (II) hospital based studies; and (III) survey- or interview-based studies with patients' self-reports.[2,3] For instance, in registry-based studies, patients can be missed due to under- and/or misdiagnosis, selection bias, incorrect registry and data management miscoding and patients who were not covered by insurance. In hospital based studies, the diagnosis is based on physical examination, which may bear a selection bias, as only patients who reaches the doctors' are included. Hospital based studies face difficulties finding an adequate control group and cannot precisely represent the community population at risk. Lastly, population-based studies are based on surveys or are interview-based, where the main risk lies in the chance of misdiagnosis of patients, and thus overestimating prevalence rates. The latter approach has the highest sensitivity, meaning that most patients will be detected, providing the possibility to gain the most epidemiological knowledge to establish a primary prevention plan. Therefore, by using the advantage of the large population-based Lifelines study including 167K participants, we aimed to figure out the prevalence of HS in the general population in the Northern Netherlands in **Chapter 2**. About 135,950 adult participants were ascertained as having HS, if they were diagnosed with HS or if they positively answered two previously validated questions to determine HS.

An overall prevalence of 2.1% was found, while thus far the overall prevalence of HS has been estimated as ~1%. Comparable to our study, higher estimated prevalence's are previously derived from prospective and self-reported studies, and lower estimates from registry-based studies.[4] However, all methodological approaches face difficulties when

interpreting prevalence data together with geographical differences in HS distributions. Consistently, the highest prevalence rates of HS are demonstrated in the Western world suggesting the influence of a Western lifestyle on the risk of HS.[5] Notably, as the highest prevalence of HS was demonstrated in Denmark (4.10%), and many low prevalence rates (≤0.30%) in the USA, the differences in health care systems and socioeconomic status may affect differences in the prevalence of HS as well.[5,6]

Zooming in at solely the medically diagnosed HS cases, the prevalence of HS would be estimated as 0.80%, indicating that HS is still strongly underdiagnosed in the Northern Netherlands. In 2015, Blok et al. showed that just 19% of HS patients were diagnosed by a general practitioner, while in the present study 46.6% of HS patients were diagnosed by their general practitioner.[7] Positively, this indicates an increased awareness of HS among general practitioners during the past years, but as more than half of the HS patients in the present study were self-diagnosed, significant progress can still be gained. For example, more patients could be reached if they will seek medical attention to a greater extent, and if on the part of the diagnosing physician, the recognition of the disease increases. Moreover, it can contribute to reducing the average diagnostic delay of 7 ~years that remains up to now a fundamental care gap.[8] Not only can this reduce the burden of HS for patients, but also the health care system could take advantage, as more expensive and invasive therapies may be evaded.[9,10]

Although it is clinically well-known that HS is associated with systematic immune-mediated diseases, yet the exact figures on these comorbidities remain to be estimated. Likewise, there is a lack of population based well-powered studies to indicate the factors associated with HS. In **Chapter 2**, next to the prevalence of HS, the epidemiology of associated comorbidities with HS was investigated. Previously reported associated comorbidities with HS were confirmed, such as Crohn's disease, diabetes type II, PCOS, depression, and anxiety. New associations with HS were identified, including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and migraine. After correcting for possible cofounders, fibromyalgia and chronic fatigue syndrome remained significantly associated with HS.

These results justify further research into comorbidities and HS, as it could provide new insights into the pathogenesis of HS. Moreover, dermatologists should screen to identify comorbid conditions in HS to mitigate their impact, especially since HS is associated with a higher comorbidity burden than psoriasis for example.[11] Comorbidity screening should include a thorough patient interview, followed by a physical examination, and optionally blood tests and/or other additional testing. Also the use of validated questionnaires should be considered, for example the PHQ-2 and PHQ-9 questionnaires to

detect depression.[12] Decision-making to screen for specific comorbidities may vary with patient risk factors, as for instance suicidality screening is recommended for HS patients with known psychiatric disease or those who exhibit signs of psychological distress.[12]

> *"Understanding the epidemiology of HS, its true prevalence, and its associated comorbidities, will contribute to the understanding of the mechanism of disease, disease risk prediction, earlier diagnosis, and intervention, and better implementation of preventive strategies."*

Considering the chronic, recurrent nature of HS, and its associated comorbidities, not surprisingly HS patients have an increased risk to suffer from mental disorders.[5,13,14] From an intuitive perspective, it is reasonable to assume that HS leads to the development of psychiatric comorbid conditions in individual patients, even though no longitudinal data exist to confirm this. In **Chapter 4**, different mental health contributing factors as loneliness and stress levels were assessed in HS patients that participated in the longitudinal Lifelines Cohort Study. Additionally, HS patients were screened for several psychiatric disorders.

Compared to the control group, patients with HS exhibited higher levels of loneliness, as measured by the shortened version of the original loneliness scale. Additionally, they reported greater levels of chronic perceived stress and a higher incidence of stressful life events, as assessed through the list of threatening experiences (LTE) and long-term difficulties inventory (LDI), respectively. According to the criteria of the Mini International Neuropsychiatric Interview, HS patients also had a more than two times higher chance of a major depressive disorder (MDD) or generalized anxiety disorder (GAD), even after adjusting for confounding factors such as sex, age, smoking, and socioeconomic status (SES). Because of the demonstrated impaired mental health of HS patients, assessments to recognize symptoms of mental disorders should be included during routine outpatient clinical practice. A golden standard questionnaire assessing mental health contributing factors, specifically validated in the HS population, could help guide the treating physician in proper detection and decision making if psychosocial support is warranted.

In order to study the causal pathway of mental health conditions in HS patients, two subgroups were distinguished from the total investigated group of HS patients: HS patients who had the diagnosis already at the time of completing the mental health questionnaires, and HS patients who developed HS later on. Surprisingly, no differences were found for any of the assessed mental health outcomes between both groups. It can therefore be hypothesized that the high prevalence of mental disorders in HS patients

should be more approached as a comorbid condition, rather than a (entire) result of the disease. For example, the high numbers of depression in HS might be (partially) attributed to systemic inflammation due to overlapping elevated proinflammatory cytokines like TNF-α, IL-12, IL-17 and IL-18, rather than to the psychosocial impact of the disease itself.[15-17]

Beneficial effects of biological treatment on depression have already been demonstrated in psoriasis, a skin disease with an overlap in cytokines (e.g. TNF-α, IL-17) in relation to HS.[18] In HS, adalimumab (anti-TNF-α) is currently the only FDA approved biological agent.[18,19] Due to the inflammatory character of HS, it is also often treated with anti-inflammatory antibiotics like doxycycline. Interestingly, the repurposing of these antibiotics has emerged as a promising therapeutic tool for mental conditions as well.[20] Understanding the underlying mechanisms of both HS and mental conditions may contribute to the discovery of new targets for the rationale of different treatment agents in HS patients suffering from mental disorders. When assessing possible improvement of mental disorders in patients, it is important to consider that the reduced symptoms of these mental conditions may not solely be attributed to the treatment. Namely, the amelioration of mental symptoms could also stem from overall disease improvement, making it challenging to distinguish if the enhanced psychological state directly results from the treatment's anti-inflammatory effect or indirectly from improved disease. In conclusion, further prospective studies are necessary to investigate the complex interaction between HS and its comorbid (mental) diseases, both at the clinical and immunological level.

> *"Screening for mental comorbidities should be part of standard care, and increased awareness of impaired mental health in the HS (outpatient) population is required. Studies assessing the effect of anti-inflammatory therapies on mental health conditions in HS patients are needed to increase understanding of comorbid mental health disorders and eventually optimize (HS) treatment."*

Lifestyle in HS

Complementary to genetic susceptibility, environmental exposures (e.g. smoking, diet, obesity and SES) forming the exposome are thought to play a key role in (the development of) HS. As the prevalence of HS seems to be higher in the Western world, where typically a Western diet is consumed (characterized by a high intake of sugar and fat and a low intake of vegetables and fruits), it can be hypothesized that unhealthy dietary habits affect the risk of HS.[21] Nonetheless, outside of three case-control studies assessing adherence of HS patients to the Mediterranean diet, and small studies focusing the possible positive effects of supplementation or decrease of dairy intake, little scientific

attention has been paid to the assessment of dietary habits and physical activity (PA) levels of HS patients. [22-25] For that reason, in **Chapter 3**, we performed a case-control study nested within the prospective Lifelines Cohort Study, and investigated the nutritional intake and PA of HS patients compared to the general population, with dietary intake of (macro)nutrients, different food groups, and dietary scores as focal points while utilizing a validated food frequency questionnaire.

According to previous studies, HS patients had a high median body mass index (BMI) of 26.1 kg/m^2 (compared to 25.3 kg/m^2 in controls). Obesity is currently considered to be a major public health burden and is associated with numerous metabolic and mechanical disorders, like HS.[26] In contrast to the elevated BMI of HS patients in our cohort, a lower median kcal intake of 1896.5 (versus 1965.2 in controls) was reported. Reasons for this discrepancy could be underreporting of the food intake of HS patients, but also their higher intake of artificially sweetened products (with a higher risk of the development of glucose intolerance) and lower compensatory levels of PA.[27] Regardless of the underlying causal factor, evidence is emerging that weight reduction solely by diminishing kilocalorie intake might not be the optimal approach, presumably due to the multi-causal etiology of obesity and metaflammation.[28,29]

Further research is of great importance to elucidate the complex issue of weight reduction in HS, especially since it has been reported that weight reduction strategies, which consequently alleviate mechanical friction, improve disease severity.[30] Contrarily, in some cases the excess skin resulting from severe weight reduction can paradoxically give rise to exacerbations of HS lesions.[30-32] Subsequently, despite the positive findings for the beneficial effects of PA in reducing disease development, and perhaps disease severity, the administration of PA in HS patients should be well-supervised. evidence suggests that PA is not only beneficial on the physical level, but also has a profound psychological impact, by lowering depression and thus improving mental health.[33] In conclusion, this gives all the more reason to intercorporate (supervised) PA in the standard treatment of HS patients.

In our study, majority of patients with HS consumed a more “Western style diet”. As this diet is known to play a role in other immune-mediated inflammatory diseases (IMIDs), this might impact HS (development). Additionally, lower dietary scores (reflected in the Lifelines diet score, alternate Mediterranean diet score, and Dutch Diet Guidelines index), indicating less adherence to dietary recommendations and subsequent consuming a lower diet quality, were associated with a higher risk of (the development) of HS as well. Ideally, specific HS diet guidelines are going to be developed being developed in the future, similar to e.g the Groningen anti-inflammatory diet (GrAID) in inflammatory

bowel disease (IBD).[34] It can be speculated given the overlapping pathways and treatments options in HS and IBD, that HS patients (at risk) might also benefit from the GrAID. Especially since high diet quality could suppress inflammatory response pathways, like the Mediterranean diet, and can help in the primary, secondary and/or tertiary prevention of HS. Also it can help to decrease the risk of depression, since pro-inflammatory diets are associated with mental diseases.[35] Although it is reported that the nutritional pattern itself is essential for the maintenance of general health and the prevention of disease, other factors, such as a sedentary lifestyle, are believed to be equally important.[36] This underlines the necessity to introduce not only the concept of e.g. the Mediterranean diet itself, but instead a balanced lifestyle as a whole (like the Mediterranean lifestyle). Initiating broad lifestyle interventions to prevent (worsening of) HS could benefit the patient therefore in multiple ways. Incorporating these alterations in the lifestyle of HS patients and their families is incredibly important. Not only can this prevent them from developing HS based on genetic predisposition, but it can also encourage HS patients to improve their lifestyle, including cessation of smoking. Nonetheless, changing patients' lifestyle habits is hard to effectuate. Due to restrictions posed by the often prevalent low SES of HS patients, they might find themselves frequently unable to procure the proper support, the right information or suitable nutrition in a timely fashion manner.

> *"As healthy diet profiles and increased PA decrease the risk of (developing) HS in the general population, novel treatment and prevention strategies should incorporate these modifiable risk factors. Patients should ideally be empowered for behavioral change and taking ownership of their lifestyle, as this will benefit them in more than one way."*

Treatment strategies in HS

With no cure for HS existing, the management of HS is symptomatic and remains elusive due to the complex etiology of HS and its heterogenous nature. Overall, unsatisfactory limited solid evidence exists for the different treatment options, supporting the need for new treatment options and more research. Several treatment modalities are available in HS treatment, including topical and oral therapies in mild disease, and reservation of biologics and surgical intervention for moderate to severe disease.

Only in 2015 the first drug, adalimumab (a TNF-α inhibitor) was approved by the FDA for the treatment of HS. To this date it is still the only registered biological for HS, with its efficacy determined based on two large clinical trials: PIONEER I (n=307) and II (n=326).[19] Here, 41.8% and 58.9% of HS patients achieved ≥50% reduction in inflammatory lesion count (HiSCR50) after 12 weeks of treatment, respectively. Compared to the efficacy demonstrated in psoriasis (71% of patients achieving PASI75 after 16 weeks), the PIONEER trials demonstrated far less efficacy.[37] Infliximab, another TNF-α inhibitor, is also used for the treatment of HS, but must be administered off-label since it is not officially registered. Only one small phase II trial in 2010 was performed including 38 HS patients who were treatment with infliximab.[38] Sixty percent of the patients on infliximab showed 25 to 50% improvement according to the HSSI score, while there was a 5.6% improvement in patients on placebo after eight weeks of treatment. A similar improvement of HS in the placebo arm was noted after cross-over. Real-world effectiveness can however not be extracted from these trials, as they use controlled settings and have strict eligibility criteria. Up to now, even though adalimumab and infliximab are widely used for years, no daily practice data existed on the real-world effectiveness of these biologics. In **Chapter 5,** the drug survival of adalimumab (n=104) and infliximab (n=44) in a daily practice cohort of HS patients was assessed in a retrospective study. Drug survival measures the length of time until discontinuation of a drug and is defined as the percentage of patients who remain on treatment. Overall drug survival of adalimumab (n=104) at 12 and 24 months was 56.3% and 30.5%, when the drug usage was discontinued mostly due to ineffectiveness. A long-term follow-up study of the patients participating in the PIONEER trials showed response maintenance in 52.3% of patients through 42 months, but these results are influenced positively as the last observation carried forward approach was used for missing data.[39]

Of note, when comparing drug survival data to drug efficacy data, it should be kept in mind that these are different outcome measures that cannot be directly compared.

For infliximab (n=44), the overall drug survival was 58.3% and 48.6% at 12 and 24 months, and was also predominantly determined by infectiveness and side-effects. Recently, another drug survival study in HS was published by Ring et al. that demonstrated rather lower (estimated) survival rates for adalimumab of ~45% % and 20%, and for infliximab of ~40% and 25% after 12 and 24 months, respectively.[40] Another small drug survival study analyzed 28 biologic-naïve HS patients treated with adalimumab, revealing an average duration of therapy of 1.34 years.[41] However, since no data regarding drug survival rates at 12 and 24 months were available, it is not possible to make a direct comparison with our data.When compared to other IMID's, the demonstrated drug survival rates in HS of both adalimumab and infliximab are remarkably lower. For example, in psoriasis the 12-month drug survival of adalimumab and infliximab ranges from 75% to 84% and from 65% to 75% in respective.[42-44] The higher drug survival rates in psoriasis could be because of the high inflammatory load in HS. Another explanation for differences in drug survival rates could be the different used dosing regimens between IMIDs. For instance, the regular HS dosing of adalimumab is 40mg s.c. every week or 80mg biweekly, while in psoriasis the standard licensed dosing is 40mg s.c. every other week. Expectably, our 12 months drug survival for side effects in adalimumab was 84.9%, in contrast to 93% in psoriasis patients treated with adalimumab as was found in a British drug survival study.[43]

Cox regression analyses showed that more severe disease was associated with a prolonged drug survival for both adalimumab and infliximab. Likewise, Gulliver et al. showed in a prospective, real-world study in 2021 that HS patients with severe disease were likely to benefit most from adalimumab treatment, with a HiSCR (at least a 50% reduction in total AN count, with no increase in abscess count, and no increase in draining fistula count relative to baseline) of ≥75% after 52 weeks.[45] As ineffectiveness is the main reason for discontinuing treatment, it is possible that surgery prolonged treatment duration by providing a local cure of disease. Surgery during treatment ($p<0.01$) was also associated with a longer survival time for infliximab, and this trend was also noticed for adalimumab. Similarly, in 2021 the SHARPS trial found that adalimumab was significantly more efficacious in combination with surgical intervention, compared to placebo.[46] Ideally, more clinical parameters should be identified to eventually create a prognostic model for treatment response of biological treatment in HS patients, as this can assist in stratifying individual patients for treatment response. As an example, a recent Italian real-world study identified an inverse correlation between therapeutic delay and clinical response to adalimumab treatment, which provides evidence encouraging early adalimumab initiation.[47] In conclusion, these results together emphasize the need for further real-world studies assessing TNF-α drug survival in HS patients and its predictive clinical parameters, preferably in a large, prospective cohort.

"Central to strategies to treat HS is the use of (early) immunosuppression, where appropriate in tandem with surgery. Enhancing knowledge about predictive clinical factors that are associated with better treatment outcomes for (biologic) therapy enables healthcare professionals to provide more effective guidance and counseling to their HS patients."

As HS was thought to be a variant of common acne in the body folds, and the old name of HS yielding acne inversa/ectopica it is therefore not surprising that retinoids for decades has been widely used as a treatment option. However, data on the performance of retinoids to treat HS are limited. Retinoids are vitamin A derivatives with anti-inflammatory and modulatory properties. Only acitretin is implied in the European HS guidelines, and retinoids are not recommended as a therapy for HS according to local Dutch guidelines.[48] Oral acitretin seems, in accordance with the European HS guidelines, to be the most promising retinoid of treatment in HS based on available studies and response rates. One case series of twelve patients even reported remission of disease and significant decrease in pain in all HS patients treated with acitretin.[49] Previous reports of isotretinoin showed variable (partial) responses on treatment of HS patients of 16.1% to 64%.[50-52] As solid evidence is missing to justify a possible role of retinoids in the treatment of HS, in **Chapter 6**, the real-world effectiveness of acitretin and isotretinoin in HS treatment was assessed. Drug survival analyses were performed of these retinoids in a retrospective daily practice HS cohort, and exploratory analyses were conducted to identify parameters associated with a longer drug survival.

A comparable 12-month treatment survival, with modest treatment survival rates of respective 44.2% and 43.8% for isotretinoin and acitretin, was found. After 24 months, acitretin showed a superior trend with a treatment survival of 39.5% compared to 15.5% for isotretinoin. Ineffectiveness and side-effects were the main reasons for discontinuing treatment, similar to the findings of our biologic drug survival study. Focusing on our drug survival rates of biologics in HS, higher treatment survival rates of 56.3% (adalimumab) and 58.3% (infliximab) after 12 months were found. Differences in treatment survival between retinoids and biologics could be explained by their treatment properties, as biologics are mainly anti-inflammatory and the effects of retinoids could be owed to different mechanisms of action. No drug survival studies have been carried out that investigated the drug survival of isotretinoin or acitretin in acne, even though both are used as a therapy against acne. In psoriasis, acitretin is a conventional treatment option as well. Several drug survival studies regarding acitretin in psoriasis have been performed, and showed a wide range of variation in 1-year acitretin survival with percentages of 37% to 79%.[53-56]

Based on clinical experience, most HS patients with acneiform phenotypes are intuitively often treated with retinoids, which indicated the role of phenotypes as a designator for deciding on which therapeutical avenue to pursue. To quantify this, Cox regression analyses were performed that included the HS phenotypes proposed by Dudink et al. (frictional furunculoid, conglobata, scarring folliculitis and regular phenotype).[57] Predictors for a longer drug survival time were the presence of comedones and concomitant medication for isotretinoin, and presence of the scarring folliculitis phenotype for acitretin. Recently, a retrospective cohort study identified also the presence of characteristics of the follicular phenotype (high number of nodules combined with the presence of multiple comedones) as a potential predictor of beneficial response for acitretin in HS.[58] These findings could be explained trough the mode of action of acitretin, since it alters keratinocyte proliferation causing a possible reduction of infundibular hyperkeratosis and follicular occlusion.[59-61] Isotretinoin on the other hand is a potent inhibitor of sebaceous gland activity, and could have led to the demonstrated association of prolonged drug survival of isotretinoin in patients with excessive comedones.[62-64] In short, our data confirms the existence of different HS phenotypes that are likely to benefit from distinct therapeutic approaches. Establishing a connection between phenotypes and genotypes holds the potential to lay the foundation for a personalized and targeted approach in future HS treatment options.

Nonetheless, a caveat that should be considered when choosing the most accurate retinoid treatment for female HS patients, is the high teratogenicity of retinoids. Adequate contraceptives should be used during treatment and at least one month after treatment for isotretinoin and even 24 months for acitretin, as conversion to etretinate is possible when exposed to alcohol. [64,65]

> *"Especially HS patients with scarring folliculitis phenotypes and highly comedogenic HS seem to particularly benefit from treatment with oral retinoids, enhancing the clinical applicability of phenotypic classifications. Differences in underlying pathomechanisms among phenotypes seem conceivable, suggesting the need of different therapeutic strategies per phenotype."*

Our drug survival studies in HS were the first attempt to understand real-world evidence in HS treatment toward achieving tailored therapy. Moreover, they showed that preferred strategies seems to exist yet in the treatment of HS. Fortunately, various novel therapies are currently being investigated for HS as potential treatment options. As the complex nature of HS pathogenesis is constantly being unraveled, this opens new rationales for therapy using biologics and small molecules. Roughly, the primary event in HS is an alteration of the hair follicle, followed by follicular occlusion and mechanical

stress causing early activation of the innate immunity of the skin.[5] Hereafter activated resident immune cells will produce pro-inflammatory cytokines, such as IL-1, IL-17, IL-12, Il-23, and TNF-α, leading to chemoattraction of other immune cells and subsequently to chronic inflammation.[66-68] Since the IL-23/Th17 pathway has repeatedly been found activated in HS lesional skin, identifying IL-23 could be seen as a promising therapeutic target. IL-23 is mainly produced by antigen-presenting cells and is composed of a p19 and p40 subunit, which bind to the IL-23 receptor on Th17 cells, and eventually produces a multitude of inflammatory cytokines. Consequently, these cytokines could be considered possible targets in the treatment of HS. For that reason, in **Chapter** 7, a phase IIa, multicenter and open-label study was conducted to evaluate the safety, tolerability, efficacy and the mode of action of guselkumab (an anti-IL-23p19 subunit monoclonal antibody) in patients with moderate-to-severe HS, named the HiGUS trial.

In the HiGUS study, adult patients received 200 mg of guselkumab subcutaneously at week 0 (baseline), 4, 8, and 12, and 16 weeks, with a 12-week follow-up period. Our trial population consisted predominantly of female, smoking HS patients with a high BMI. As these characteristics reflect the typical outpatient population, it thereby increases the relevance of our results for daily, real-life practice. Of the twenty included HS patients that completed our study, 65% achieved HiSCR after 16 weeks of treatment. In addition, the median IHS4 score decreased significantly from 8.5 to 5.0, and the median inflammatory nodule and abscess (AN) count was significantly reduced from 6.5 to 4.0 points. Compared to adalimumab, the PIONEER I and II studies showed somewhat less efficacy with respectively 41.8% and 58.9% of HS patients achieving HiSCR.[19] In comparison to ustekinumab (the most widely used IL-12/IL-23 inhibitor), our study showed also better clinical efficacy in HS, as in a small open label study of Blok et al. found 47% of HS patients achieved HiSCR.[69] Interestingly, in moderate-to-severe psoriasis, which shares common pathogenesis pathways with HS, guselkumab demonstrated also superior efficacy in head-to-head comparator trials vs. adalimumab, ustekinumab and secukinumab.[70]

In addition to the assessment of disease characteristics, patient-reported outcomes (PROMs) were investigated. No significant differences after 16 weeks of treatment were found, but patient treatment satisfaction was rated at a median of 8 (out of 10), with a higher scoring standing for higher satisfaction. A small recent drug survival study assessing IL-23 therapy in HS did found positive impact on HS patients' quality of life (QoL), as measured by the Dermatology Life Quality Index (DLQI), similar to the HiGUS study.[71]

Even though the HiGUS trial showed modest improvement of disease, preliminary results of the NOVA trial (a phase IIb randomized controlled trial investigating the efficacy of guselkumab in HS of n=181, NCT03628924) seem to have less optimistic results. In

their treatment arm, 45.0% and 50.8% of HS patients treated with guselkumab achieved HiSCR, depending on the received treatment regimens (1200 mg guselkumab i.v. at weeks 0, 4, and 8, and 200 mg guselkumab s.c. at week 12, or 200 mg guselkumab s.c. at weeks 0, 4, 8, and 12, respectively). Subsequently, 38.7% of the HS patients in the control arm achieved HiSCR. In HS, more frequently high placebo rates are demonstrated in clinical trials, like in the PIONEER I and II adalimumab trials (placebo rates of respective 26.0% and 27.6%).[70] Accordingly, a systematic review by Amir Ali et al. concluded a higher placebo effect in randomized clinical trials (RCTs) of therapies in HS, than in RCTs for psoriasis and eczema.[72] Possible explanations include the dynamic character of HS itself including flares, study design, but also surroundings factors like taking extra care of patients during a trial. Extra care of patients during a trial could optimize the physician-patient relationship and may result is better treatment adherence, or encouragement toward beneficial lifestyle changes. The high placebo effects in HS studies underline als the need for psychological interventions in the management of HS once more.

Another pitfall when interpreting data from clinical trials in HS, is the evaluation of disease severity and treatment outcome. The multiple outcome measure instruments that have been used in HS RCTs lack validation data, and no golden standard exists yet to assess HS disease severity and treatment outcome, hampering the interpretation of treatment efficacy and comparisons between studies.[73] Most clinical trials in HS use HiSCR as outcome instrument, however a substantial limitation of this tool is its lack of being able to dynamic measure draining tunnels, resulting in several clinical HS trials not meeting their primary endpoint.[74] This emphasizes the need for an universally accepted, validated, easy to use, and preferably timesaving assessment tool to use in daily practice and a clinical trial setting. For example, Tzellos et al. recently developed and validated a new dichotomous assessment tool (the IHS4-55), based on the International Hidradenitis Suppurativa Severity Score System (IHS4), a continuous score that incorporates inflammatory nodules, abscesses and draining tunnels to overcome the main pitfall of the HiSCR of not accounting for draining tunnels.[75] Due to the recurrent nature of HS, a longitudinal measurement over multiple days or weeks rather than at one time point, might be the best option to measure treatment outcome. Currently, more core outcome measure instruments for HS trials are being developed and evaluated by the international HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC) initiative to determine the most important outcomes in HS. [76]

Globally, the quality of evidence to support the use of biologics in HS is limited, as has been demonstrated by our HiGUS study as well. HS treatment remains burdensome, with no one size fits all solution and an unpredictable response to medical treatment. Besides guselkumab, all other treatment options in HS with high-level evidence struggle

to accomplish adequate disease control as well. Several antibodies targeting various molecules have been proposed for HS, but there is often an unpredictable and unsatisfactory response to these treatment options. One can argue that to optimize treatment outcomes, HS patients need to be stratified according to clinical or immunological predictive biomarkers. Nonetheless, up to date no biomarkers with adequate clinical applicability in HS have been identified. Additionally, the distribution and concentration of therapeutic antibodies (biologics) in the skin are unknown because no methods are available to measure these values directly. Fluorescence molecular imaging might pave the way as a new modality to overcome this challenge, as it entails a mechanism where a fluorescent dye linked to a biological agent creates a fluorescence signal in the diseased tissue that can be visualized and quantified with dedicated optical fluorescence imaging systems. It would not only be able to help gain insight in the biologic distribution in inflammatory (skin) diseases like HS, but could also function as a tool for proper therapy designation for specific biological therapies, in discerning optimal dosage regimens, and eventually in more cost-effective healthcare. Only in 1996 Stringer et al. described a study of 15 psoriasis patients that investigated the accumulation of a photosensitizing agent in areas of plaque psoriasis by monitoring the fluorescence emission.[77] No other studies researching fluorescent molecular imaging in skin disorders have been carried out thus far, but in other diseases, such as cancer and inflammatory bowel disease, fluorescence molecular imaging is currently being investigated and has shown promising preliminary results.[78-82]

"No silver bullet has been identified yet in the treatment of HS. Emerging new therapies, like anti IL-23 treatment, can expand treatment options in HS and lay the first stone for an evidence-based, personalized medicine approach, possibly in combination with novel imaging techniques such as fluorescence imaging."

Future perspectives

From this thesis it can be extrapolated that HS is an underreported complex skin disorder in which factors such as the exposome and immune system are involved. Moreover, HS is linked to a high comorbidity burden including mental health comorbidities, and disease management poses challenges for both treating physicians and patients.

Due to the shown underreported prevalence in the Northern Netherlands, strategies to enhance earlier recognition and correct diagnosis, directed to health care professionals and predisposed individuals, should be designed. To reach this goal in the Netherlands, the HiCare project is launched by the Erasmus Medical Center Rotterdam and the University Medical Center Groningen, with the aim to focus on creating a regional collaboration of dermatologists involved in HS patient care. Treatment protocols are created based on the refined Hurley classification and clear referral guidelines are established (data not published). Schultheis et al. recently described already the beneficial effects of the establishment of standardized treatment algorithms for HS on the course of the disease.[83]

Furthermore, it seems that a more holistic approach might be suited to manage HS. To exemplify, not only should the medical management focus on disease management, but also on management of comorbidities, both physical and mental. Highlighting impaired mental health in HS patients might improve adherence to therapy, and subsequently disease course. Recommendations how to screen for these are urgently needed to incorporate the best management approach for HS. Another interesting topic that potentially can change prevention and clinical management of HS are lifestyle modifications such as diet and PA. No evidence based dietary recommendations are currently available in HS, even though nutrition is likely to contribute to the etiology of HS. Dietary intervention studies in HS patients (and their household members) are of vital importance, preferably as randomized controlled trials and meta-analyses. For example, studies could be designed in which HS patients receive food-boxes adhering to an anti-inflammatory diet including counselling with a dietician to expand knowledge of the role of nutrition as a pathophysiological factor in HS. Following this thesis, an eHealth application (myH-Scoach) is currently being developed in which HS patients can fill out questionnaires. Here, a Food Frequency Questionnaire and other questionnaires assessing lifestyle factors such as PA can be implemented. This can not only be used in the secondary or tertiary prevention of HS, but can also be applied as a tool in the primary prevention for susceptible individuals. Besides addressing the role of nutrition in (the development of) HS, it should be considered to involve a specialized physiotherapist in the prevention and the management of HS. Up to now, no recommendations regarding physiotherapy in HS prevention or treatment are existing due to the knowledge gap on this topic with high quality evidence lacking. To pursue a broader prevention and treatment panel

for HS, reliable algorithms need to be developed including lifestyle and psychological based recommendations.

Complementary to lifestyle alterations, a combination of different treatments are likely to be necessary in the battle against HS because of its heterogeneous nature. Focusing on combining therapies in a holistic patient-tailored manner, instead of concentrating on one treatment option might be the best option. Combining treatment targets with different biologicals, which is widespread practice in other IMIDs like IBD, might be needed to optimize treatment outcomes. Currently, many more novel drugs with new immunological targets are being investigated for HS, and later this year secukinumab is expected to be registered for HS. JAK-inhibitors have also the potential to regulate several cytokines involved in the pathogenesis of HS, as theoretically they do hold promise in regulating various inflammatory cascades and thus modify disease in a beneficial manner. According to clinicaltrials.gov many phase II trials are nearing completion at the moment, vindicating the expansion of the therapeutic pipeline for HS (see for an overview of current treatment options and possible upcoming therapies **Figure 1**). Head-to-head well designed and properly executed phase III and IV trials are warranted to ameliorate this debilitating disease further, preferably through RCTs that examine not only monotherapy, but also combination therapies as can be carried out by extending study arms. Moreover, real-world studies are necessary to enhance daily practice applicability, better treatment differentiation and a more individual tailored therapy. So forth, it will be possible for the future physician to instigate a more evidence-based systemic biologic regimen.

Unfortunately, current HS treatment strategies aim for reaching only HiSCR50, which entails roughly 50% improvement of disease, while in other IMIDs like psoriasis 90% or even 100% improvement of disease is pursued. Once more, this emphasizes the need of therapies that are potent enough to reach higher degrees of disease improvement, such as HiSCR75, HiSCR90 and in the end HiSCR100. Hopefully, next to adapting different therapeutic options to different HS phenotypes, identification of predictive biomarkers can assist to achieve these therapeutical endpoints. Because the discovery of universal predictive biomarkers can ultimately instigate the development of more personalized HS treatment approaches, there is need to identify reliable and predictive biomarkers in HS. Integrating fluorescence molecular imaging in HS may lay the first stone for radical improvement of treating HS patients, as it can incorporate patient risk stratification, and clinical factors in therapeutical decision making. In doing so it enables the treating physicians to accurately tailor their therapy to the individual HS patients' need in their journey to beat HS.

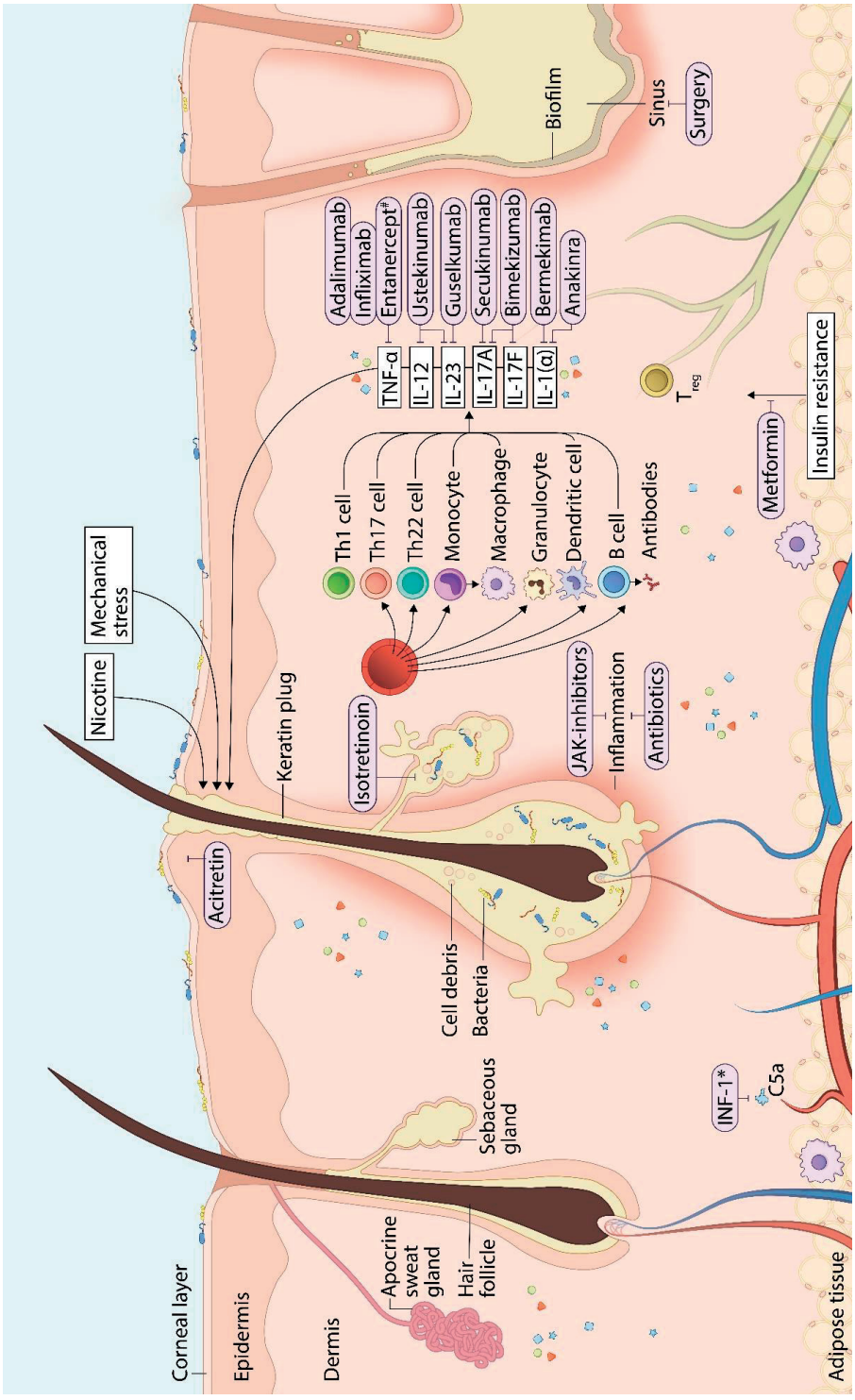

Figure 1. *Current HS treatment options and several therapies of interest.*

REFERENCES

1. Savage KT, Gonzalez Brant E, Flood KS, Salian P, Porter ML, Kimball AB. Publication trends in hidradenitis suppurativa from 2008 to 2018. *J Eur Acad Dermatol Venereol*. Sep 2020;34(9):1885-1889. doi:10.1111/jdv.16213
2. Zimman S, Comparatore MV, Vulcano AF, Absi ML, Mazzuoccolo LD. Hidradenitis Suppurativa: Estimated Prevalence, Clinical Features, Concomitant Conditions, and Diagnostic Delay in a University Teaching Hospital in Buenos Aires, Argentina. *Actas Dermosifiliogr (Engl Ed)*. May 2019;110(4):297-302. Hidradenitis supurativa: una aproximacion a su prevalencia, caracteristicas clinicas, comorbilidades y tiempo al diagnostico, en un hospital universitario de Buenos Aires, Argentina. doi:10.1016/j.ad.2019.01.004
3. Jemec GB, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. *J Am Acad Dermatol*. Aug 1996;35(2 Pt 1):191-4. doi:10.1016/s0190-9622(96)90321-7
4. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol*. May 2020;82(5):1045-1058. doi:10.1016/j.jaad.2019.08.090
5. Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers*. Mar 12 2020;6(1):18. doi:10.1038/s41572-020-0149-1
6. Matusiak L. Profound consequences of hidradenitis suppurativa: a review. *Br J Dermatol*. Dec 2020;183(6):e171-e177. doi:10.1111/bjd.16603
7. Blok JL, Boersma M, Terra JB, et al. Surgery under general anaesthesia in severe hidradenitis suppurativa: a study of 363 primary operations in 113 patients. *J Eur Acad Dermatol Venereol*. Aug 2015;29(8):1590-7. doi:10.1111/jdv.12952
8. Saunte DM, Boer J, Stratigos A, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. *Br J Dermatol*. Dec 2015;173(6):1546-9. doi:10.1111/bjd.14038
9. Marvel J, Vlahiotis A, Sainski-Nguyen A, Willson T, Kimball A. Disease burden and cost of hidradenitis suppurativa: a retrospective examination of US administrative claims data. *BMJ Open*. Sep 30 2019;9(9):e030579. doi:10.1136/bmjopen-2019-030579
10. Kirby JS, Miller JJ, Adams DR, Leslie D. Health care utilization patterns and costs for patients with hidradenitis suppurativa. *JAMA Dermatol*. Sep 2014;150(9):937-44. doi:10.1001/jamadermatol.2014.691
11. Reddy S, Strunk A, Garg A. Comparative Overall Comorbidity Burden Among Patients With Hidradenitis Suppurativa. *JAMA Dermatol*. Jul 1 2019;155(7):797-802. doi:10.1001/jamadermatol.2019.0164
12. Garg A, Malviya N, Strunk A, et al. Comorbidity screening in hidradenitis suppurativa: Evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. *J Am Acad Dermatol*. May 2022;86(5):1092-1101. doi:10.1016/j.jaad.2021.01.059
13. Machado MO, Stergiopoulos V, Maes M, et al. Depression and Anxiety in Adults With Hidradenitis Suppurativa: A Systematic Review and Meta-analysis. *JAMA Dermatol*. Aug 1 2019;155(8):939-945. doi:10.1001/jamadermatol.2019.0759
14. Crowley JJ, Mekkes JR, Zouboulis CC, et al. Association of hidradenitis suppurativa disease severity with increased risk for systemic comorbidities. *Br J Dermatol*. Dec 2014;171(6):1561-5. doi:10.1111/bjd.13122
15. Kohler CA, Freitas TH, Maes M, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand*. May 2017;135(5):373-387. doi:10.1111/acps.12698

16. Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. *Neuron*. Jul 22 2020;107(2):234-256. doi:10.1016/j.neuron.2020.06.002
17. Misitzis A, Goldust M, Jafferany M, Lotti T. Psychiatric comorbidities in patients with hidradenitis suppurativa. *Dermatol Ther*. Jul 2020;33(4):e13541. doi:10.1111/dth.13541
18. Patel N, Nadkarni A, Cardwell LA, et al. Psoriasis, Depression, and Inflammatory Overlap: A Review. *Am J Clin Dermatol*. Oct 2017;18(5):613-620. doi:10.1007/s40257-017-0279-8
19. Kimball AB, Okun MM, Williams DA, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med*. Aug 4 2016;375(5):422-34. doi:10.1056/NEJMoa1504370
20. Chaves Filho AJM, Mottin M, Soares MV, Juca PM, Andrade CH, Macedo DS. Tetracyclines, a promise for neuropsychiatric disorders: from adjunctive therapy to the discovery of new targets for rational drug design in psychiatry. *Behav Pharmacol*. Apr 1 2021;32(2&3):123-141. doi:10.1097/FBP.0000000000000585
21. Christ A, Latz E. The Western lifestyle has lasting effects on metaflammation. *Nat Rev Immunol*. May 2019;19(5):267-268. doi:10.1038/s41577-019-0156-1
22. Barrea L, Fabbrocini G, Annunziata G, et al. Role of Nutrition and Adherence to the Mediterranean Diet in the Multidisciplinary Approach of Hidradenitis Suppurativa: Evaluation of Nutritional Status and Its Association with Severity of Disease. *Nutrients*. Dec 28 2018;11(1)doi:10.3390/nu11010057
23. Danby FW. Diet in the prevention of hidradenitis suppurativa (acne inversa). *J Am Acad Dermatol*. Nov 2015;73(5 Suppl 1):S52-4. doi:10.1016/j.jaad.2015.07.042
24. Choi F, Lehmer L, Ekelem C, Mesinkovska NA. Dietary and metabolic factors in the pathogenesis of hidradenitis suppurativa: a systematic review. *Int J Dermatol*. Feb 2020;59(2):143-153. doi:10.1111/ijd.14691
25. Lorite-Fuentes I, Montero-Vilchez T, Arias-Santiago S, Molina-Leyva A. Potential Benefits of the Mediterranean Diet and Physical Activity in Patients with Hidradenitis Suppurativa: A Cross-Sectional Study in a Spanish Population. *Nutrients*. Jan 27 2022;14(3)doi:10.3390/nu14030551
26. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. Jul 6 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
27. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. Oct 9 2014;514(7521):181-6. doi:10.1038/nature13793
28. Maarouf M, Platto JF, Shi VY. The role of nutrition in inflammatory pilosebaceous disorders: Implication of the skin-gut axis. *Australas J Dermatol*. May 2019;60(2):e90-e98. doi:10.1111/ajd.12909
29. Mintoff D, Agius R, Benhadou F, Das A, Frew JW, Pace NP. Obesity and Hidradenitis Suppurativa: Targeting meta-inflammation for therapeutic gain? *Clin Exp Dermatol*. May 12 2023;doi:10.1093/ced/llad182
30. Sivanand A, Gulliver WP, Josan CK, Alhusayen R, Fleming PJ. Weight Loss and Dietary Interventions for Hidradenitis Suppurativa: A Systematic Review. *J Cutan Med Surg*. Jan/Feb 2020;24(1):64-72. doi:10.1177/1203475419874412
31. Boer J. Resolution of hidradenitis suppurativa after weight loss by dietary measures, especially on frictional locations. *J Eur Acad Dermatol Venereol*. May 2016;30(5):895-6. doi:10.1111/jdv.13059
32. Macklis PC, Tyler K, Kaffenberger J, Kwatra S, Kaffenberger BH. Lifestyle modifications associated with symptom improvement in hidradenitis suppurativa patients. *Arch*

Dermatol Res. Apr 2022;314(3):293-300. doi:10.1007/s00403-021-02233-y

33. Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. *Neurosci Biobehav Rev*. Dec 2019;107:525-539. doi:10.1016/j.neubiorev.2019.09.040
34. Campmans-Kuijpers MJE, Dijkstra G. Food and Food Groups in Inflammatory Bowel Disease (IBD): The Design of the Groningen Anti-Inflammatory Diet (GrAID). *Nutrients*. Mar 25 2021;13(4)doi:10.3390/nu13041067
35. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: A systematic review and meta-analysis. *Clin Nutr*. Oct 2019;38(5):2045-2052. doi:10.1016/j.clnu.2018.11.007
36. Diolintzi A, Panagiotakos DB, Sidossis LS. From Mediterranean diet to Mediterranean lifestyle: a narrative review. *Public Health Nutr*. Oct 2019;22(14):2703-2713. doi:10.1017/S1368980019000612
37. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. Jan 2008;58(1):106-15. doi:10.1016/j.jaad.2007.09.010
38. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. Feb 2010;62(2):205-17. doi:10.1016/j.jaad.2009.06.050
39. Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. Jan 2019;80(1):60-69 e2. doi:10.1016/j.jaad.2018.05.040
40. Ring HC, Maul JT, Yao Y, et al. Drug Survival of Biologics in Patients With Hidradenitis Suppurativa. *JAMA Dermatol*. Feb 1 2022;158(2):184-188. doi:10.1001/jamadermatol.2021.4805
41. Saal RC, Alnaif S, Edwards JF, Wintringham JA, Smith RJ. Real-world drug survival of patients with hidradenitis suppurativa treated with adalimumab. *JAAD Int*. Jun 2023;11:209-210. doi:10.1016/j.jdin.2023.03.004
42. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol*. Jan 2015;172(1):244-52. doi:10.1111/bjd.13343
43. Warren RB, Smith CH, Yiu ZZN, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol*. Nov 2015;135(11):2632-2640. doi:10.1038/jid.2015.208
44. Menting SP, Sitaram AS, Bonnerjee-van der Stok HM, de Rie MA, Hooft L, Spuls PI. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. *Br J Dermatol*. Oct 2014;171(4):875-83. doi:10.1111/bjd.13001
45. Gulliver W, Alavi A, Wiseman MC, et al. Real-world effectiveness of adalimumab in patients with moderate-to-severe hidradenitis suppurativa: the 1-year SOLACE study. *J Eur Acad Dermatol Venereol*. Dec 2021;35(12):2431-2439. doi:10.1111/jdv.17598
46. Bechara FG, Podda M, Prens EP, et al. Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa: The SHARPS Randomized Clinical Trial. *JAMA Surg*. Nov 1 2021;156(11):1001-1009. doi:10.1001/jamasurg.2021.3655

47. Marzano AV, Genovese G, Casazza G, et al. Evidence for a 'window of opportunity' in hidradenitis suppurativa treated with adalimumab: a retrospective, real-life multicentre cohort study. *Br J Dermatol*. Jan 2021;184(1):133-140. doi:10.1111/bjd.18983
48. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. Apr 2015;29(4):619-44. doi:10.1111/jdv.12966
49. Boer J, Nazary M. Long-term results of acitretin therapy for hidradenitis suppurativa. Is acne inversa also a misnomer? *Br J Dermatol*. Jan 2011;164(1):170-5. doi:10.1111/j.1365-2133.2010.10071.x
50. Huang CM, Kirchhof MG. A New Perspective on Isotretinoin Treatment of Hidradenitis Suppurativa: A Retrospective Chart Review of Patient Outcomes. *Dermatology*. 2017;233(2-3):120-125. doi:10.1159/000477207
51. Patel N, McKenzie SA, Harview CL, et al. Isotretinoin in the treatment of hidradenitis suppurativa: a retrospective study. *J Dermatolog Treat*. Jun 2021;32(4):473-475. doi:10.1080/09546634.2019.1670779
52. Soria A, Canoui-Poitrine F, Wolkenstein P, et al. Absence of efficacy of oral isotretinoin in hidradenitis suppurativa: a retrospective study based on patients' outcome assessment. *Dermatology*. 2009;218(2):134-5. doi:10.1159/000182261
53. Chularojanamontri L, Silpa-Archa N, Wongpraparut C, Limphoka P. Long-term safety and drug survival of acitretin in psoriasis: a retrospective observational study. *Int J Dermatol*. May 2019;58(5):593-599. doi:10.1111/ijd.14349
54. Arnold T, Schaarschmidt ML, Herr R, Fischer JE, Goerdt S, Peitsch WK. Drug survival rates and reasons for drug discontinuation in psoriasis. *J Dtsch Dermatol Ges*. Nov 2016;14(11):1089-1099. doi:10.1111/ddg.13152
55. Shalom G, Zisman D, Harman-Boehm I, et al. Factors associated with drug survival of methotrexate and acitretin in patients with psoriasis. *Acta Derm Venereol*. Nov 2015;95(8):973-7. doi:10.2340/00015555-2130
56. Davila-Seijo P, Dauden E, Carretero G, et al. Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. *J Eur Acad Dermatol Venereol*. Nov 2016;30(11):1942-1950. doi:10.1111/jdv.13682
57. Dudink K, Aarts P, Ardon CB, et al. Prevalence and Clinical Characteristics of Hidradenitis Suppurativa Phenotypes in a Large Dutch Cohort. *Dermatology*. 2022;238(3):600-602. doi:10.1159/000518965
58. Sanchez-Diaz M, Diaz-Calvillo P, Rodriguez-Pozo JA, Arias-Santiago S, Molina-Leyva A. Effectiveness and Safety of Acitretin for the Treatment of Hidradenitis Suppurativa, Predictors of Clinical Response: A Cohort Study. *Dermatology*. Aug 23 2022:1-8. doi:10.1159/000526019
59. Doran TI, Shapiro SS. Retinoid effects on sebocyte proliferation. *Methods Enzymol*. 1990;190:334-8. doi:10.1016/0076-6879(90)90038-3
60. Lu L, Lai H, Pan Z, et al. Clinical and histopathological characteristics in patients with scarring folliculitis type of acne inversa. *Dermatoendocrinol*. 2017;9(1):e1361575. doi:10.1080/19381980.2017.1361575
61. van der Zee HH, Jemec GB. New insights into the diagnosis of hidradenitis suppurativa: Clinical presentations and phenotypes. *J Am Acad Dermatol*. Nov 2015;73(5 Suppl 1):S23-6. doi:10.1016/j.jaad.2015.07.047
62. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol*. Oct

2006;126(10):2178-89. doi:10.1038/sj.jid.5700289

63. Tsukada M, Schroder M, Roos TC, et al. 13-cis retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-trans retinoic acid and binding to retinoid acid receptors. *J Invest Dermatol*. Aug 2000;115(2):321-7. doi:10.1046/j.1523-1747.2000.00066.x
64. Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother*. Aug 2005;6(10):1725-34. doi:10.1517/14656566.6.10.1725
65. Layton AM, Dreno B, Gollnick HP, Zouboulis CC. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. *J Eur Acad Dermatol Venereol*. Aug 2006;20(7):773-6. doi:10.1111/j.1468-3083.2006.01671.x
66. Frew JW, Hawkes JE, Krueger JG. A systematic review and critical evaluation of immunohistochemical associations in hidradenitis suppurativa. *F1000Res*. 2018;7:1923. doi:10.12688/f1000research.17268.2
67. Gudjonsson JE, Tsoi LC, Ma F, et al. Contribution of plasma cells and B cells to hidradenitis suppurativa pathogenesis. *JCI Insight*. Oct 2 2020;5(19)doi:10.1172/jci.insight.139930
68. Vossen A, van der Zee HH, Tsoi LC, et al. Novel cytokine and chemokine markers of hidradenitis suppurativa reflect chronic inflammation and itch. *Allergy*. Mar 2019;74(3):631-634. doi:10.1111/all.13665
69. Blok JL, Li K, Brodmerkel C, Horvatovich P, Jonkman MF, Horvath B. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol*. Apr 2016;174(4):839-46. doi:10.1111/bjd.14338
70. Light JG, Su JJ, Feldman SR. Clinical Utility of Guselkumab in the Treatment of Moderate-to-Severe Plaque Psoriasis. *Clin Cosmet Investig Dermatol*. 2021;14:55-63. doi:10.2147/CCID.S235242
71. Repetto F, Roccuzzo G, Burzi L, et al. Drug Survival of Anti Interleukin-17 and Interleukin -23 Agents after Adalimumab Failure in Hidradenitis Suppurativa: A Pilot Study. *Acta Derm Venereol*. Apr 19 2023;103:adv5278. doi:10.2340/actadv.v103.5278
72. Amir Ali A, Seng EK, Alavi A, Lowes MA. Exploring changes in placebo treatment arms in hidradenitis suppurativa randomized clinical trials: A systematic review. *J Am Acad Dermatol*. Jan 2020;82(1):45-53. doi:10.1016/j.jaad.2019.05.065
73. Ingram JR, Hadjieconomou S, Piguet V. Development of core outcome sets in hidradenitis suppurativa: systematic review of outcome measure instruments to inform the process. *Br J Dermatol*. Aug 2016;175(2):263-72. doi:10.1111/bjd.14475
74. Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol*. Dec 2014;171(6):1434-42. doi:10.1111/bjd.13270
75. Tzellos T, van Straalen KR, Kyrgidis A, et al. Development and validation of IHS4-55, an IHS4 dichotomous outcome to assess treatment effect for hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. Oct 2 2022;doi:10.1111/jdv.18632
76. Thorlacius L, Ingram JR, Villumsen B, et al. A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. *Br J Dermatol*. Sep 2018;179(3):642-650. doi:10.1111/bjd.16672
77. Stringer MR, Collins P, Robinson DJ, Stables GI, Sheehan-Dare RA. The accumulation of protoporphyrin IX in plaque psoriasis after topical application of 5-aminolevulinic acid indicates a potential for superficial

photodynamic therapy. *J Invest Dermatol*. Jul 1996;107(1):76-81. doi:10.1111/1523-1747.ep12298282

78. Atreya R, Neumann H, Neufert C, et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. *Nat Med*. Mar 2014;20(3):313-8. doi:10.1038/nm.3462
79. Rath T, Bojarski C, Neurath MF, Atreya R. Molecular imaging of mucosal alpha4beta7 integrin expression with the fluorescent anti-adhesion antibody vedolizumab in Crohn's disease. *Gastrointest Endosc*. Aug 2017;86(2):406-408. doi:10.1016/j.gie.2017.01.012
80. van Dam GM, Themelis G, Crane LM, et al. Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-alpha targeting: first in-human results. *Nat Med*. Sep 18 2011;17(10):1315-9. doi:10.1038/nm.2472
81. van der Laan JJH, van der Waaij AM, Gabriels RY, Festen EAM, Dijkstra G, Nagengast WB. Endoscopic imaging in inflammatory bowel disease: current developments and emerging strategies. *Expert Rev Gastroenterol Hepatol*. Feb 2021;15(2):115-126. doi:10.1080/17474124.2021.1840352
82. Vahrmeijer AL, Hutteman M, van der Vorst JR, van de Velde CJ, Frangioni JV. Image-guided cancer surgery using near-infrared fluorescence. *Nat Rev Clin Oncol*. Sep 2013;10(9):507-18. doi:10.1038/nrclinonc.2013.123
83. Schultheis M, Staubach P, Nikolakis G, et al. A centre-based, ambulatory care concept for Hidradenitis suppurativa improves disease activity, burden, and patient satisfaction: results from the randomised controlled trial EsmAiL. *Br J Dermatol*. May 3 2023;doi:10.1093/bjd/ljad135