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BIOLOGICAL AND SURGICAL TREATMENT OF SEVERE HIDRADENITIS SUPPURATIVA

Dominique C. van Rappard
BIOLOGICAL AND SURGICAL TREATMENT OF SEVERE HIDRADENITIS SUPPURATIVA

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prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 13 oktober 2015 om 14.00 uur

door

Dominique Carlette van Rappard
geboren te Nijmegen
**PROMOTIECOMMISSIE:**

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Faculteit der Geneeskunde
CHAPTER 1

General introduction and aims of this thesis
1. HISTORY

Hidradenitis suppurativa (HS), which literally translates from Greek as 'purulent inflammation of the sweat glands', is a devastating, recurrent skin disease. Two French surgeons were the first to recognize this disease more than one and a half century ago. In 1839, Velpeau described chronic, inflammatory abscesses in the axillae, around the mammae and in the perianal area. He named the disease 'lhidrosadénite phlegmoneuse', which is French for HS. In 1939, almost a century later, Brunsting suggested a specific role for the apocrine sweat glands, rather than the eccrine glands, due to the preferred location of disease. Half way the 20th century Shelly and Cahn demonstrated keratinous plugging and inflammation of the apocrine sweat glands, through a small experiment applying sticky tape on the axillae of 12 patients. In 1989, the term acne inversa was introduced, suggesting a secondary role for the sweat glands in the pathogenesis, after hyperkeratinisation of the infundibulum, similar to acne. Later studies confirmed this interpretation. Although technically a misnomer, the term HS is nowadays still most frequently used in literature, followed by acne inversa, acne ectopica and Verneuil’s disease.

2. EPIDEMIOLOGY

The prevalence of HS varies in literature from approximately 0.05% to 4%, and is averagely estimated around 1%. Women are more commonly affected than men (3:1). The disease typically occurs after puberty, in the second and third decade of life and seems to decrease over time, with a lower prevalence among those of 55 years and older. Patients with a positive family history of HS seem to develop lesions at a younger age. There is no clear racial predilection, although some studies point to a higher prevalence in individuals of African descent.

3. ETIOLOGY

3.1 Pathogenesis

The exact cause of HS is still unknown and most probably multifactorial. The primary event in the pathogenesis is believed to be follicular hyperkeratosis with plugging and dilatation of the pilosebaceous unit, rupture and extrusion of follicular contents, including keratin, corneocytes, bacteria and sebaceous matter into the dermis. Subsequently, inflammation, abscess and sinus tract formation can occur. The apocrine involvement appears to be a secondary phenomenon.

3.2 Smoking and obesity

Smoking and obesity are two well-established risk factors in the development of HS. Approximately 80-90% of the HS patients smokes or has a history of smoking. A positive correlation for disease severity was found for smokers versus non-smokers with HS.
In line with this finding, Schrader et al. described that a patient’s number of smoking pack-years, has an influence on disease severity. In addition, a new term ‘smoker’s boils’ was proposed, to alert patients that this condition is potentially avoidable. However, another study failed to recognize any correlation between smoking and disease severity. Obesity is also a frequently observed risk factor in patients with HS. Canoui-Poitrine et al. showed a strong association between body mass index (BMI) and disease severity. Also, reduction of severity has been observed in patients undergoing bariatric surgery resulting in weight loss of more than 15% of their total bodyweight. Smoking or high BMI may both reduce the chance of eventual remission of disease.

3.3 Friction and irritation

Another proposed factor that can aggravate the condition is mechanical friction, which contributes to HS development by promoting follicular occlusion and by triggering rupture of dilated follicles. HS is generally located in areas of regular friction. Also, this can be illustrated by HS lesions in the additional abdominal folds, or on the medial upper legs in obese patients.

Furthermore, patients mention sweating, heat, stress, fatigue and tight clothing as aggravating factors. The contribution of chemical depilatories, deodorants, and talcum powder as a trigger factor for HS could not be demonstrated in research.

3.4 Infection

The exact role of bacteria in the etiology of HS remains controversial. Bacterial cultures of HS are frequently sterile. Previous microbiological studies found a wide range of bacteria sporadically associated with HS lesions, including Staphylococcus and Streptococcus. Interpretation of the results of bacteriological examinations from the surface of HS lesions is obscured by the possible contamination of resident skin bacteria. Some studies used a carbon dioxide (CO2) laser method allowing sampling of bacteriological cultures from deeper HS parts. These examinations showed several species, most frequently coagulase-negative staphylococci. Bacteria probably do not have a causative role, but rather are considered to be contaminants of primarily inflammatory lesions. Furthermore, the absence of serious infectious complications, such as cellulitis and abnormal lymph nodes does not support a role for bacterial infection.

3.5 Hormones

A role for hormones in the pathogenesis of HS is suggested due to the tendency of the disease’ pre-menstrual flare-ups, female predominance, improvement during pregnancy, and the rarity of the disease before puberty and post-menopausal. A role for hormones was advocated by Stellon et al. who noticed a link between initiation of treatment with certain combined oral contraceptives and the onset of HS, possibly due to the progestogens in these contraceptives. Additionally, Mortimer et al. found
a higher concentration of total testosterone in HS patients than in a control group without HS. The same authors also found a positive effect of anti-androgen therapy. A positive effect of finasteride has also been suggested. However, reports on this subject are contradicting. Numerous other studies failed to find a significant difference in the androgen metabolism or signs of androgenization between HS patients and matched controls. Barth et al. found no difference in plasma androgens in women with HS compared to controls matched for BMI and hirsuties.

3.6 Genetics

A positive family history is reported by 35-40% of the HS patients. In 1985, Fitzsimmons et al. systematically investigated the genetic basis of HS in 26 families and observed an autosomal dominant inheritance pattern with a variable penetrance. This was later confirmed by von der Werth et al. In 2006, Gao et al. showed that the disease gene of HS is located on chromosome 1p21.1-1q25.3 in a study that involved a four generation Chinese family. However, another study failed to confirm this link in two Indian families, and emphasized that HS is genetically heterogeneous and that more than one genomic region is responsible for disease phenotype.

Lately specific gene mutations of presenilin (PSEN), presenilin enhancer 2 (PSENEN), and nicastrin (NCSTN) were identified as being responsible for familial HS, with NCSTN being the most commonly observed. The clinical phenotype of all reported mutation-positive cases is severe and extensive. PSEN, PSENEN and NCSTN, together with anterior pharynx defective 1 (APH1), form the γ-secretase complex. γ-Secretase cleaves type 1 transmembrane proteins, including amyloid precursor protein and Notch. An increase in the length of β-amyloid peptides produced by cleavage of amyloid precursor protein, form cerebral plaques and is therefore associated with Alzheimer’s disease. Genetic inactivation of γ-secretase in mouse skin produces follicular plugging, which is similar to the follicular plugging observed in human HS. These mice developed abscesses in the inguinal, perianal, and retroauricular areas. This is probably due to the altered Notch signaling. Within the epidermis, Notch signaling is involved in epidermal cell differentiation and, hair follicle differentiation, and controls epidermal proliferation (tumor suppressor function). A decrease in tumor suppressor function may explain why mice also developed squamous cell carcinoma (SCC) in some lesions, which is also a rare complication of HS in cases that disease persists for a long time.

3.7 Immune dysregulation

Several studies suggest that HS is a disease of immune dysregulation. HS is associated to other immune mediated diseases like pyoderma gangrenosum (PG) or Crohn’s disease. This theory is supported by the fact of positive response of HS to TNF-α inhibitors and other immunosuppressive therapies.
A variety of cytokines has been investigated, and the evidence to date is somewhat conflicting. These conflicting results may be caused by variations in disease activity or in investigative approaches. The trend appears to be toward an increased expression of TNF-α, IL-1β, IL-10, IL-17, IL-23 and IL-12 in HS. These results provide potential therapeutic targets, other than the broadly investigated TNF-α inhibitors.

Additionally, immune mediators regulate antimicrobial proteins (AMPs) expression in the skin and several studies suggest involvement of AMPs in the pathogenesis of HS. AMPs play an important role in the cutaneous defense against bacteria and are produced by keratinocytes. Because cutaneous AMPs represent a major line of defense against skin infections, a relative AMP deficiency may be responsible for bacterial propagation in HS lesions.40

3.8 Associations and comorbidities
Besides smoking and obesity, more comorbidities have been linked to HS, but causality remains to be explored, and not all reports are in agreement. A recent large study of 1776 HS patients observed significantly more comorbidities in HS patients compared with control, including hypertension, dyslipidemia, arthropathies and polycystic ovarian syndrome, in an adjusted analysis.10 Crowley et al. demonstrated an association with depression and morbid obesity, after controlling for possible confounding variables, but failed to find an association with hypertension.41 Yet another study also failed to identify hypertension to be associated with HS. Furthermore, the authors were not able to find an association with diabetes mellitus and dyslipidemia.8 However, a more recent report associated HS with metabolic syndrome (diabetes mellitus, hypertension, dyslipidemia and obesity).42

HS and co-occurring (skin) diseases are broadly mentioned in literature. Well-known is the so-called follicular occlusion triad, consisting of HS, dissecting folliculitis of the scalp and acne conglobata.43 Together with pilonidal sinus it is named the follicular occlusion tetrad.44 Other less frequently observed diseases that have been linked to HS in scarce case-reports include keratitis-ichthyosis-deafness syndrome, Dowling-Degos disease, pachyonychia congenita, interstitial keratitis, Behçet’s disease, and Fox-Fordyce disease.45

More frequently, the association of HS with PG has been described. PG is a rare neutrophilic dermatosis, characterized by acute and progressive ulcerative skin lesions. Every part of the body can be affected, but the ulcers are predominantly seen on the legs. Both PG and HS are implicated in recently suggested syndromes like PASH (pyoderma gangrenosum, acne, suppurative hidradenitis), PASS (pyoderma gangrenosum, acne conglobata, suppurative hidradenitis, and spondyloarthritis), PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne), and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis).46 Additionally, HS is sometimes seen as part of SAPHO (synovitis, acne, pustulosis, hyperosteosis, osteitis) syndrome.47

As the above-mentioned syndromes indicate, HS has been associated with rheumatologic symptoms (spondyloarthropathy). Spondyloarthropathy includes a spectrum of related disorders comprising the prototype ankylosing spondylitis, a subset
of psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthropathy. An association among HS, acne conglobata and arthritis in 10 patients was described in 1982. Since then, several cases of HS and co-occurrence of arthritis have been published. These include axial as well as peripheral arthritis, and occasionally enthesopathy. The exact frequency of arthritis in HS is unknown.

Since 1991 several case-reports have described the co-occurrence of Crohn’s disease and HS. Subsequently, the prevalence of HS in patients with inflammatory bowel disease has been estimated in larger groups. These data show a prevalence of HS of up to 26% for patients with Crohn’s disease and of 18% for patients with ulcerative colitis, suggesting a possible association. Crohn’s disease generally precedes HS with several years.

SCC may be considered to be a severe complication of HS, probably due to chronic inflammatory status. Several cases of HS and subsequent SCC have been described. Noticeably, there is a male predominance (4:1) and there is a predilection of the buttock and perianal area, in which 61% of the SCC cases are present. On average, HS is present 25 years before the development of the SCC.

4. Diagnosis

4.1 Clinical features

HS is a purulent chronic skin disease. Three diagnostic criteria have been proposed for establishing the diagnostic of HS, including 1) typical lesions, 2) typical topography, 3) chronicity and recurrences.

In most instances the first lesion is a painful, deep-seated nodule, or blind boil without central necrosis. Usually the lesion will progress to an abscess, sometimes followed by spontaneously purulent drainage, with temporary relief of pain. The disease has a tendency to recur, with more similar lesions appearing in adjacent skin. Subsequent characteristics are linear or angular shaped sinus tracts (Fig. 1) with permanent malodorous discharge. Due to chronic inflammation, typical hypertrophic fibrous ‘bridging’ scars can occur, which may decrease limb mobility. Furthermore, open comedos can be present.

Figure 1. HS lesion of the buttocks with sinus tracts.
The most commonly affected topographies are the inverse areas of the body or apocrine-gland-bearing skin (Fig. 2). The groin is most frequently affected, followed by the axillae and the perianal, gluteal, and submammary regions. Atypical locations involve the nape of the neck, the waist, and the periumbilical and retroauricular regions (Fig. 3). The areas that are typically involved differ for male and female patients. The front of the body, including the submammary and inguinal areas, is predominantly affected in female patients, while the back of the body, including the perianal and gluteal areas, is more often affected in male patients. Axillary involvement has no gender predilection. Male patients seem to be more severely affected than female patients.

4.2 Histology

Early lesions consist of follicular hyperkeratosis with plugging and dilatation of the hair follicle, typically followed by superficial and deep folliculitis and abscess formation. Inflammatory infiltrate consist of neutrophils, lymphocytes and histiocytes. Inflammation of apocrine glands occurs secondarily and only in a minority of specimens. In one study, secondary apocrine gland involvement was found in 12% of specimens and secondary involvement of eccrine glands was found in 25%. Biopsies of established HS show sinus tracts lined by stratified squamous epithelium, containing keratin. In adjacent

Figure 2. Typical distribution of HS lesions. (a) The perianal and gluteal region, (b) the groin, and (c) the axilla.
tissue, extensive fibrosis is often present. The formation of granulation tissue with inflammatory cells and occasional foreign body giant cells can be present.

4.3 Grading

The severity of HS is most frequently ranked by using the Hurley’s grading system. This system defines three degrees of severity, mainly based on the presence and extent of cicatrization and sinuses (Table 1 and Fig. 4). The majority of HS patients in the general population has Hurley grade I. A quarter of the patients has grade II, and only a small minority has grade III. The Hurley grading system can be useful for overall classification of cases and may form the basis for the selection of appropriate treatment. A recent publication observed that patients are capable of scoring their own disease severity according to Hurley, using photographs.

A more precise scoring system to assess HS severity was proposed by Sartorius in 2003. This Sartorius score takes into account the number of anatomic zones involved, the number and scores of individual lesions, the longest distance between two lesions, and whether the lesions are separated by normal-appearing skin. A higher score indicates a more severe disease. It has a wide range, starting at zero with no upper limit. The Sartorius score has been modified and is used in numerous clinical trials. It turned out to have a good correlation to the broadly used Hurley stages, with a low inter-observer variability, and seems to be suitable for monitoring the effects of treatment.

Recently, a valid practical clinical endpoint was proposed, the HS Clinical Response (HiSCR). Its purpose is to define responders of treatment, that can be easily used in trials. HiSCR achievers were defined as: 1) at least 50% reduction of abscesses or nodules, 2) no increase in the number of abscesses and 3) no increase in the number of draining fistulas from baseline.
Table 1. Hurley classification

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<td>I</td>
<td>Abscess formation, single or multiple without sinus tracts and cicatrization.</td>
</tr>
<tr>
<td>II</td>
<td>Recurrent abscesses with tract formation and cicatrization. Single or multiple, widely separated lesions.</td>
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<tr>
<td>III</td>
<td>Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area.</td>
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Additionally, the HS Physician’s Global Assessment (HS-PGA) is easily and frequently used as clinical measure for assessing HS. The Dermatology Life Quality Index (DLQI) and de Visual Analog Scale (VAS)-pain score are frequently used as patients reported outcomes.

4.4 Quality of life

The quality of life impairment for patients with HS is significant. It was found to be even higher than in some other dermatoses including psoriasis, atopic dermatitis, acne vulgaris, alopecia, chronic urticaria and neurofibromatosis. Not surprisingly, the impact of HS on quality of life shows positive correlation with the severity of the disease. Matusiak et al. found average DLQI scores of 5.8, 13.1, and 20.4 for Hurley I, II, and III respectively.

5. TREATMENT

5.1 Topical

Several studies investigated the efficacy of topical clindamycin. One randomized controlled trial (RCT) of 30 patients investigated the use of topical clindamycin 1% solution twice daily versus placebo and found a significant reduction in papules and pustules, but not of inflammatory nodules or abscesses. A subsequent double-blind RCT compared topical clindamycin 1% solution twice daily with oral tetracycline 500 mg twice daily in 46 patients and found no significant difference in efficacy between the two treatments.

Resorcinol has been used in treatment of HS due to its keratolytic effect and is available in several concentrations. In 2010 de Boer et al. found resorcinol 15% to be
5.2 Systemic

5.2.1 Antibiotics

Although antibiotics are widely used to treat HS, limited data on their efficacy are available. Besides their bactericidal effects, antibiotics used for HS also have immunomodulatory properties.

Apart from the comparison of systemic tetracyclines with topical clindamycin, no systematic research has been done to establish the efficacy of tetracyclines. However, some case-reports suggest improvement of HS.

Yet, three retrospective studies and one prospective study investigated the role of clindamycin in combination with rifampicin during a 10 week study period. The majority of patients was treated with 600 mg clindamycin and 600 mg rifampicin daily. A beneficial effect was demonstrated in all studies. Improvement of disease was noticed in 71-86% of the patients. The incidence of side effects accompanying this treatment strategy ranged from 13-38% between studies, mainly digestive symptoms, like diarrhea.

5.2.2 Retinoids

Isotretinoin appears generally ineffective in HS, in contrast to its effectiveness in acne. In a retrospective study of 88 patients, who received oral isotretinoin for a mean duration of 7.8 months and an average daily dose of 44 mg, an improvement was reported in only 16.1%, no effect in 77.0%, and worsening in 6.9%. These data are in accordance with an earlier publication that concluded that isotretinoin mono-therapy (average dose of 0.56 mg/kg/day during 4-6 months) for patients with HS usually has a limited therapeutic effect.

Acitretin, another retinoid compound, has also been investigated and seems effective in several small studies. A recent publication of Matusiak et al. showed a good response in almost half of the patients, who were treated with an average daily dose of 0.56 mg/kg, for up to 9 months. However, relapses did occur in nearly all patients after cessation of drug administration. This is in contrast to the study by Boer and Nazary who observed therapy success in all 12 patients treated with acitretin for 9-12 months, and who found long-term improvement with effects lasting up to 4 years after discontinuation of treatment.

The discrepancy between the efficacy of acitretin and isotretinoin can be explained pharmacologically. Namely, acitretin induces normalization of epithelial cell proliferation and differentiation, which prevents the primary event in the pathogenesis of HS, follicular plugging. In contrast, isotretinoin is ineffective, as this agent primarily works on sebaceous glands, which are not involved in the pathogenesis of HS.
5.2.3 Hormones

In one RCT hormonal therapy based on antiandrogen cyproterone acetate and ethinyloestradiol proved to be useful for HS. In another retrospective cohort study, the efficacy of antiandrogen therapy was compared to that of antibiotics. The response to antiandrogen therapy was superior to that of antibiotics (55% vs 25%). Also finasteride has been investigated, and several case-series report a positive effect. One study found that six out of seven patients (2 male, 5 female) improved significantly, and three of them had complete healing of their lesions. Two patients experienced remissions lasting 8-18 months.

5.2.4 Immunosuppressives

5.2.4.1 Biologicals

There have been reports of promising results of the treatment of HS with anti-tumor necrosis factor-alpha (anti-TNF-α). TNF-α is an important pro-inflammatory cytokine that is essential for the induction and maintenance of the inflammatory immune response. It is a signaling molecule that regulates processes like proliferation, survival, differentiation and apoptosis. It can be produced by different cells, though mainly by macrophages.

Three biologicals have been broadly investigated for the treatment of HS, namely infliximab, etanercept and adalimumab. These biologicals have been approved by the Food and Drug Administration for the treatment of several other inflammatory (skin) diseases, for example rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis. But until now, HS has remained a condition for which TNF-α inhibitors are used only as ‘off-label’ treatment.

The first beneficial effect of anti-TNF-α was reported in a study in 2001, which described improvement of HS lesions after three infliximab infusions in a patient with Crohn’s disease and coexisting HS. Subsequently, the first report on etanercept appeared in 2004, and the first on adalimumab in 2005. In 2009, a systematic search to evaluate the three biologics was performed by Haslund et al. They found a positive treatment outcome in 45 out of 52 infliximab patients, 35 out of 37 etanercept patients, and 16 out of 16 adalimumab patients. Recently, more articles, including RCTs, confirmed the efficacy of infliximab and adalimumab, but failed to prove the efficacy of etanercept.

Due to these promising results, the research of other potentially effective biologicals continues. Two studies, which together included a total of four patients evaluated the effect of ustekinumab, an IL-12/23 inhibitor. Two patients showed a significant response, one patient showed only a moderate response, and one patient did not respond at all. Also, anakinra, an IL-1 receptor antagonist, shows conflicting results in several case-reports. One patient with severe HS showed failure of anakinra therapy and subsequently also failed to respond to golimumab, another TNF-α antibody. An additional open-label study showed a positive result in all five patients.
treated with anakinra. Efalizumab, which targets CD11a, was investigated in a study of five patients and seemed to be ineffective. Efalizumab was withdrawn from the market in 2009 because of side-effects.

5.2.4.2 Others

Fumarates have been investigated in a group of seven patients with recalcitrant HS, of which three patients showed clinically meaningful improvement.

Methotrexate was not effective for three patients treated with 12.5-15 mg weekly for 1.5-6 months.

Colchicine, normally used as an anti-inflammatory drug in gout, was investigated by van der Zee et al. Eight HS patients were treated with the accepted gout regimen of 0.5 mg colchicine twice a day up to 4 months, in an open prospective pilot study. No clinically relevant improvement of disease severity was observed.

Three case studies on cyclosporine are available, which together included four patients who were treated with 2-6 mg/kg during 4-6 months. A significant response was observed in half of the patients.

The largest of the three available studies on the use of dapsone for HS, included 24 patients in a prospective trial who were treated with 50–200 mg/day. Improvement was seen in nine out of 24 treated patients (38%), whereas 15 out of 24 (62%) did not experience any improvement. Recurrence rapidly occurred after treatment discontinuation.

5.3 Surgical and other invasive treatments

5.3.1 Surgery

Although patients with chronic HS often benefit from long-term systemic medical treatment, surgery is often necessary to fully cure this recurrent condition, and is therefore regarded as a crucial step. While surgery is regarded as the most effective treatment for HS, there is lack of RCTs, and studies are generally of retrospective design.

Various surgical techniques are used in HS patients, such as incision and drainage, deroofing, CO2 laser surgery, and excision followed by various wound closure methods. Incision and drainage offers only temporary relief, and lesions almost invariably recur. This can be useful in acute settings when patients present themselves with extremely painful fluctuant abscesses. Deroofing consists of removal of the ‘roofs’ of sinus tracts with preservation of the bottom of the tracts, which leads to fast re-epithelialization. CO2 laser ablation is believed to be a tissue-saving technique in which repeated vaporization of affected skin is performed.

The mainstay of surgical management remains complete excision of affected tissue while leaving clear margins. No consensus exists on the ideal extent of the margins used for excisions. In mild cases limited excision can be used (Fig. 5). For more advanced disease most authors recommend a wider margin of 1-3 cm into healthy tissue, or total removal of all hair-bearing tissue.
Several different wound closure techniques can be used, with the optimal choice based on the extent of the defect after surgery, the location, and the experience of the surgeon. These include: primary closure (Fig. 6), secondary closure using split-skin grafts (Fig. 7), or local or distant flaps, or healing by secondary intention.

There is no consensus on the most suitable surgical technique for HS. Studies on this subject are very heterogeneous in terms of disease severity, patient numbers, disease location, surgical techniques, and follow-up time, which makes indirect comparison difficult.92

A recently published guideline on treatment of HS listed several larger studies concerning various surgical management techniques, showing recurrence rates of 17% for deroofing, 21-70% for excision, 1-12% for CO2 laser, and 14% for electro-surgery.93

Concerning wound closure techniques, the same guideline cited recurrence rates of 32% for secondary healing, 34% for primary closure, 21-33% for grafts, and 19% for flaps.93

For example, a study of 31 patients by Ritz et al. found recurrence rates of 100% after incision and drainage (median time 3 months), of 43% after limited excision (median time 11 months), and of 27% after wide excision (median time 20 months).89 Mandal and Watson found a recurrence rate of 70% for patients treated with surgery and primary closure, and no recurrence for the ‘graft’ and ‘flap’ series.94

Figure 5. Limited surgery. (a) Abscess of the right axilla treated with (b) excision yielding pus, (c) in an outpatient setting.

Figure 6. (a) HS of the right axilla. (b) Excision of affected tissue leaving clear margins. (c) Primary closure of the wound.
On the other hand, Buyukasik et al. reported no recurrences in their series of 20 primary closure cases, with a mean follow-up time of 42 months.\textsuperscript{95} Also, Rompel and Petres found only 2.5\% recurrence in a group of 106 patients after wide excision, with a median follow-up duration of 36 months, and claimed that the method of reconstruction had no influence on the recurrence.\textsuperscript{96}

In a very recent study of Mikkelsen et al. CO2 laser-treated lesions recurred in 29\% of the 58 patients, within 12 months on average. They found obesity to be a significant risk factor for recurrence.\textsuperscript{91}

\textbf{Figure 7.} HS treated with split-skin grafting. (a) Extensive HS lesions of the right groin. (b) The left upper leg is used as a donor site. (c) Large defect of the right groin and a square superficial defect of the donor site. (d) The split-skin graft is used to cover the defect. Also notice that the left groin (a) has been treated earlier with the same technique and hence acts as an illustration of the final result.
Morgan et al. compared skin grafting and healing by granulation with Silastic foam dressing, in 10 patients with bilateral axillary HS, in split-body study.\textsuperscript{97} Although grafting resulted in more rapid healing, most patients preferred granulation, due to the good cosmetic result, the avoided need for immobilization and the lack of a painful donor site.

### 5.3.2 Other invasive treatments

Besides the use of the ablative CO\textsubscript{2} laser as a surgical tool, other non-ablative lasers have been used for the treatment of HS. Their main target is destruction of the hair follicle unit. Mahmoud et al. conducted a randomized, right-left within-patient controlled trial in 22 patients.\textsuperscript{98} Patients were treated monthly for a period of 4 months with the Nd:YAG laser. Significantly more improvement was seen on the laser-treated side. The treatment was associated with minimal patient discomfort, and 60% of the patients did not experience pain related to laser treatment.

Intense pulsed light (IPL) is another treatment for HS, which causes thermal damage to the follicle, resulting in hair removal. In a RCT of 18 patients conducted by Highton et al., one side of the body was treated with IPL and the contra lateral side received no treatment.\textsuperscript{99} A significant improvement was seen for all treated sites.

The use of aminolaevulinic acid (ALA)-photodynamic therapy (PDT) for the treatment of HS has shown varying success rates in several case-series.\textsuperscript{93} A recently conducted RCT advocated the use of niosomal methylene blue gel, as a photosensitizer delivered as a niosomal gel and activated by IPL, in a split-body study.\textsuperscript{100}

Several case-reports claim good effects of botulinum toxin injections, and explain the injections’ effectiveness by their prevention of a moist environment and therefore of bacterial overgrowth.\textsuperscript{101} Another theory that may explain the effectiveness of botulinum toxin, is that it switches off the function of the whole pilosebaceous unit.

Radiotherapy has been used in several series in the past with various results. In a study of 231 patients by Fröhlich et al., radiotherapy resulted in complete relief in 38% and in improvement in 40% of the patients.\textsuperscript{102} Only two patients did not respond. However, due to the possible carcinogenic side effects of this treatment, it should be considered with great caution.

Bong et al. claimed that eight of their 10 patients benefited from treatment with cryosurgery. A major drawback was the significant pain that most patients experienced during and after treatment. Eight patients had post-treatment ulceration, infection, or both. The average post-operation healing time was 25 days.\textsuperscript{103}

### 6. AIMS OF THIS THESIS

HS is a common, purulent skin disease with a great impact on patients’ lives. In recent years, there is more attention for this devastating skin disease, and the number of scientific publications on this subject is rapidly expanding. HS is generally perceived as a difficult skin disease to treat. A patient with severe HS is a challenge for every
physician. In this thesis we focus mainly on the treatment of severely affected patients, based on biological as well as a surgical approaches.

A variety of treatment methods is available for HS, but only a few of those are based on high quality evidence. The aim of Chapter 2 is to give an overview of the currently available evidence for the pharmacological as well as invasive treatment modalities of HS. We perform a systematic review that includes only RCTs and we critically evaluate them.

The etiology of HS is still not completely understood. In Chapter 3 we further investigate this by performing a study of a possible genetic factor that could cause HS. It is our hypothesis that polymorphisms in the CARD15/NOD2, as expressed in Blau Syndrome and Crohn's disease, may have a comparable role in HS. We will analyze the entire coding region of the CARD15/NOD2 gene in six patients with a high 'pre-test probability' of having a genetic factor.

The current interpretation of the clinical features of HS is extended in Chapter 4. We propose a new entity: a rare clinical variant of HS, which has not been described in literature before. This variant presents itself as a plaque form that may occur on all parts of the body.

Chapters 5, 6, and 7 cover studies that focus specifically on the biological treatment of HS with TNF-\(\alpha\) inhibitors. In Chapter 5 we compare the efficacy and safety of the two most widely used biologicals in the treatment of HS, namely infliximab and adalimumab. We compare two cohorts of 10 adult patients suffering from severe, recalcitrant HS. In Chapter 6 we perform a systematic search, to provide an overview of the current evidence regarding off-label treatment of HS with TNF-\(\alpha\) inhibitors. This systematic review covers all types of articles on infliximab, etanercept or adalimumab. It also includes our findings based on the treatment of our own patients, who are described in Chapter 5 and 7. In Chapter 7 we describe the remarkable observation that some HS patients develop arthritis after treatment with infliximab, as an adverse event. We perform a retrospective study to establish the frequency and clinical presentation of new onset arthritis during infliximab treatment.

In Chapter 8 we present another promising off-label indication for treatment with TNF-\(\alpha\) inhibitors. We report six patients with pyoderma gangrenosum, who were treated with infliximab.

In Chapter 9 and 10 we investigate the surgical approach of HS, as surgery is considered to be a crucial step to eventually cure the condition. The efficacy and patient satisfaction of local excision followed by primary closure is determined in Chapter 9, based on the questioning of 57 patients. Eventually, in Chapter 10 we gather our knowledge from the earlier chapters and study 30 patient who were treated with the combined approach of biological treatment (infliximab) and additional surgical interventions.
REFERENCES

22. Lapins J, Jarstrand C, Emtestam L. Coagulase-negative staphylococci are the most common bacteria found in cultures from the deep portions of hidradenitis suppurativa lesions, as obtained by carbon dioxide laser surgery. Br J Dermatol 1999; 140: 90-5.


CHAPTER 2

Randomized controlled trials for the treatment of hidradenitis suppurativa

D.C. van Rappard, J.R. Mekkes, T. Tzellos

Dermatologic Clinics 2015, in press
ABSTRACT

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease. A variety of treatment modalities is available for HS, but most of them lack high quality evidence. A systematic search was performed to identify all randomized controlled trials for the treatment of HS in order to systematically review and critically evaluate current available evidence. Eleven randomized controlled trials were selected and critically appraised. The studies involved biologics, antibiotics, hormonal therapy, laser and surgical treatment. Indirect comparison is not possible because different efficacy outcomes are used. Recommendations for future randomized controlled trials include use of validated scores, like HiSCR, inclusion of patient rated outcomes, like DLQI, TWPI and thorough report of side effects. Evidence for long term treatment and benefit risk ratio of available treatment modalities is highly needed in order to enhance evidence based treatment in daily clinical practice. Combining surgery with anti-inflammatory treatment is a concept that warrants further investigation.
INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, scarring, debilitating skin disease, which usually presents after puberty. It presents with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas, most commonly the axillae, inguinal and anogenital regions. HS also inflicts a significant burden on patients and is associated with comorbid diseases like pyoderma gangrenosum, arthritis, anemia, significantly reduced quality of life, depression, stigmatization, inactivity, working disability, and impairment of sexual health. Epidemiological studies also highlight that HS patients present several cardiovascular risk factors, such as smoking, obesity, dyslipidemia (low HDL and hypertriglyceridemia), diabetes, and metabolic syndrome, at a significantly higher rate compared to healthy controls. The above mentioned evidence indicates that HS is far more than a disease limited to skin and that it displays systemic chronic inflammation characteristics, like psoriasis.

Hurley stage, Modified Sartorius Score (MSS) and HS Physician’s Global Assessment (HS-PGA) are measures that have been used to classify and assess HS disease severity (Box 1). Hurley staging (Table 1) classifies HS into 3 stages and has been proposed as a tool to facilitate rational treatment decision making in a certain body location. The MSS requires assessment of number and type of inflammatory and non-inflammatory lesions in 7 anatomical regions, measurement of the longest distance between 2 lesions of the same type in each anatomical region and identification of involvement of Hurley stage III lesions for each region. It is a time consuming score that can be difficult to apply in daily clinical practice and includes lesions (scar), which may not be sensitive to medical treatment. Lastly, HS-PGA (Table 2) was developed and includes 6 stages with clear guidance for disease severity assessment. It is also easier to use than MMS. Because MMS is impractical to use in daily clinical practice, assessment of Hurley stage and HS-PGA seems more appropriate to guide decision making.

Box 1. How to evaluate HS patients

<table>
<thead>
<tr>
<th>Classification/severity assessment:</th>
<th>Comorbidities assessment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hurley stage</td>
<td>• Quality of life (DLQI)</td>
</tr>
<tr>
<td>• Modified Sartorius score</td>
<td>• Pain (VAS)</td>
</tr>
<tr>
<td>• HS Physician’s Global Assessment</td>
<td>• Smoking</td>
</tr>
<tr>
<td></td>
<td>• Obesity (BMI, WC)</td>
</tr>
<tr>
<td></td>
<td>• Metabolic syndrome (NCEP-ATP III)</td>
</tr>
<tr>
<td></td>
<td>• Diabetes</td>
</tr>
<tr>
<td></td>
<td>• Anemia</td>
</tr>
<tr>
<td></td>
<td>• Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>• Work productivity (WPAI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment effectiveness assessment:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• HiSCR (inflammatory manifestations)</td>
<td></td>
</tr>
<tr>
<td>• Inflammatory nodules, abscesses and draining fistulas count</td>
<td></td>
</tr>
<tr>
<td>• Modified Sartorius score</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; DLQI, dermatology life quality index; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; NCEP-ATP III, national cholesterol education program adult treatment panel III criteria; VAS, visual analogue scale; WC, waist circumference; WPAI, work productivity and activity impairment questionnaire.
A valid and easy-to-use clinical outcome for assessing treatment efficacy is essential to objectively and uniformly evaluate treatments and enhance evidence-based clinical practice. Taking into account that the previously used scores for HS severity assessment exhibit several drawbacks, like inability to accurately assess the extent of inflammation within each stage, difficulty to use and interpret, and measurement inconsistency, a new score was recently developed, evaluated and validated as a clinical outcome for assessment of treatment effectiveness, especially for the inflammatory manifestations: the Hidradenitis Suppurativa Clinical Response (HiSCR). The HiSCR requires counting inflammatory nodules, abscesses and draining fistulas at baseline and after the intervention. Improvement is defined as 1) at least 50% reduction in the number of abscesses and inflammatory nodules, 2) no increase in the number of abscesses, and 3) no increase in the number of draining fistulas from baseline. HiSCR was significantly correlated with improvements in all physician and patient-rated outcomes. Thus, the use of this validated, easy-to-use score is recommended to be used in both research and daily clinical practice. Assessment of comorbidities at baseline is highly needed, in order to promote a holistic treatment approach. Quality of life should be determined with the Dermatology Life Quality Index (DLQI). Pain assessment should be included, preferably with scales like Visual Analogue Scale (VAS). As evidence for association of HS with metabolic

### Table 1. Hurley staging

<table>
<thead>
<tr>
<th>Hurley stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Abscess formation, single or multiple, without sinus tracts and cicatization</td>
</tr>
<tr>
<td>II</td>
<td>Single or multiple, widely separated, recurrent abscesses with tract formation and cicatization</td>
</tr>
<tr>
<td>III</td>
<td>Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area</td>
</tr>
</tbody>
</table>

### Table 2. Hidradenitis Suppurativa - Physicians Global Assessment

| Clear (score=0) | 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules |
| Minimal (score=1) | 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules |
| Mild (score=2) | 0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules; or 1 abscess or draining fistula and 0 inflammatory nodules |
| Moderate (score=3) | 0 abscesses, 0 draining fistulas, and ≥ 5 inflammatory nodules; or 1 abscess or draining fistula and ≥ 1 inflammatory nodule; or 2–5 abscesses or draining fistulas and < 10 inflammatory nodules |
| Severe (score=4) | 2–5 abscesses or draining fistulas and ≥ 10 inflammatory nodules |
| Very severe (score=5) | > 5 abscesses or draining fistulas |
syndrome and cardiovascular risk factors accumulate, a thorough baseline assessment and screening of cardiovascular risk factors and identification especially of the modifiable ones is also advisable. Presence of superinfections should be evaluated. Laboratory tests and cultures are at the discretion of the examining physician and based on patient history and clinical findings. As part of broad-based approach, HS patients should be offered adjuvant therapy regarding pain management, weight loss, tobacco cessation, treatment of superinfections, and application of appropriate dressings.

A variety of treatment methods are available for HS, but only a few of them are based on high quality evidence. The aim of this article is to give an overview of the currently available evidence for the pharmacological as well as invasive treatment modalities of HS. This will facilitate rational decision making in daily clinical practice and elucidate recommendations for future randomized clinical trials.

METHODOLOGY
In order to objectively identify all randomized controlled clinical trials (RCTs) for the treatment of HS, a systematic search was undertaken in the electronic databases MEDLINE, EMBASE and CENTRAL up to January 30th 2015, using a draft search strategy for RCTs for MEDLINE (OVID), as suggested in the Cochrane Handbook. Eligible criteria were RCTs, which included patients with HS. Other study designs than RCTs, were excluded. Also conference abstracts and review articles were excluded. There was a restriction for the English language. Information from each study was extracted using a standardized data extraction form. To assess the methodological quality, the “Risk of bias” tool suggested in the Cochrane Handbook for Systematic Reviews of Interventions was used. The following items were critically appraised and extracted: method of generation of the randomization sequence, allocation concealment, blinding of participants, researchers, and outcome assessors, incomplete outcome data (attrition bias), and selective reporting (reporting bias). In addition, the baseline characteristics of study groups were checked for confounding factors in order to rule out selection bias.

RESULTS
The systematic search provided 197 results. After screening, 11 studies met the inclusion criteria. The selection process is summarized in Fig. 1. General study characteristics are summarized in Table 3 and the most important results in Table 4. Four studies involved biological therapy with anti-tumor necrosis factor-alpha (anti-TNF-α). Two studies investigated the role of antibiotics, and one study investigated hormonal therapy. Also three studies on laser, and one study of surgical treatment were included. The methodological quality of all studies are separately presented in Fig. 2 and pooled together in a graph in Fig. 3.
Biologics

The first RCT that appeared on biologics for HS, involved infliximab, followed by one study on etanercept.\textsuperscript{19,20} Subsequently two studies investigated the efficacy of adalimumab.\textsuperscript{11,22} The positive effect of infliximab treatment was found by Grant et al.\textsuperscript{20} who studied 38 patients in a well-conducted, double-blinded trial, during 52 weeks. Patients received infliximab (5 mg/kg at weeks 0, 2, and 6, and subsequently every 8 weeks) or placebo. After 8 weeks the double-blind phase was followed by an open-label phase where patients taking placebo were given the opportunity to cross-over. More patients in the infliximab group showed a 50% or greater decrease from baseline in HS severity score (a non-validated composite scoring system), when compared to placebo at week 8, although this difference in improvement was not significant (27% vs 5%, \textit{p}=0.092). However, infliximab was significantly more effective on PGA, VAS, DLQI, and in producing 25-50% improvement on HS severity score. Also, a significant reduction in inflammatory markers was observed at week 8. Infliximab monotherapy was well tolerated, and a greater number of adverse events occurred in the placebo group. Adverse events in the infliximab group were mild and included influenza-like illness, myalgia, dizziness, and headache. Also two serious adverse events were reported, including pregnancy and hypertension. Adverse events in the placebo group included nausea, influenza-like illness, pyrexia, nasopharyngitis, and dizziness. One serious adverse event occurred, namely an infusion reaction.

Etanercept turned out to be not effective in a small RCT. Adams et al.\textsuperscript{19} investigated 20 patients assigned to either etanercept 50 mg subcutaneously twice a week, or placebo for 12 weeks. Subsequently, all patients received open-label etanercept for 12 more weeks.

\textbf{Figure 1.} Flow diagram of the search strategy. Eleven randomized controlled clinical trials were identified and included in this review. The general characteristics of these studies are included in Table 3.
There was no statistically significant difference in PGA between treatment and placebo group (p>0.99). Also, none of the secondary outcomes, including PGA and DLQI, were significantly improved. The only adverse drug reactions reported were mild injection site reactions, unclear if this occurred in both groups. A limitation of the study is the small, unjustified sample size and the simply brief description of trial design and outcome.

In case of adalimumab, Miller et al. \(^\text{22}\) initially studied 21 patients with moderate to severe HS, in a double-blinded, placebo controlled trial. Actively treated patients received adalimumab 80 mg s.c. at baseline followed by 40 mg s.c. every other week for 12 weeks. A significant reduction was seen in Sartorius score after 6 weeks but not after 12 weeks (-10.7 vs. 7.5, p=0.02 and -11.3 vs. 5.8, p=0.07) when compared to the placebo group. None of the secondary endpoints, including VAS pain and
Table 3. Characteristics of randomized controlled trials for the treatment of HS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Setting</th>
<th>Methods</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemmensen 1983</td>
<td>Denmark</td>
<td>Single-center, double-blind, placebo-controlled</td>
<td>30 HS patients Hurley I and mild Hurley II</td>
</tr>
<tr>
<td>Mortimer 1986</td>
<td>UK</td>
<td>Single-center, double-blind, controlled, cross-over</td>
<td>24 F HS patients with moderate to severe HS</td>
</tr>
<tr>
<td>Jemec 1998</td>
<td>Denmark</td>
<td>Single-center, randomized, double-blind, controlled</td>
<td>46 HS patients (39F, 7M), Hurley I and II</td>
</tr>
<tr>
<td>Buimer 2007</td>
<td>Netherlands</td>
<td>Single-center, randomized, controlled</td>
<td>200 HS patients</td>
</tr>
<tr>
<td>Mahmoud 2009</td>
<td>USA</td>
<td>Single-center, randomized, controlled split-body</td>
<td>22 HS patients (19F, 3M), Hurley II</td>
</tr>
<tr>
<td>Adams 2010</td>
<td>USA</td>
<td>Single-center, randomized, double-blind, placebo-controlled</td>
<td>20 HS patients with moderate to severe HS</td>
</tr>
<tr>
<td>Grant 2010</td>
<td>USA</td>
<td>Single-center, randomized, double-blind, placebo-controlled</td>
<td>38 HS patients with moderate to severe HS</td>
</tr>
<tr>
<td>Highton 2011</td>
<td>UK</td>
<td>Single-center, randomized, controlled split-body</td>
<td>18 HS (15F, 3M) patients, Hurley II and III</td>
</tr>
<tr>
<td>Miller 2011</td>
<td>Denmark</td>
<td>Two-center, randomized, double-blind, placebo-controlled</td>
<td>21 HS patients with moderate to severe HS</td>
</tr>
<tr>
<td>Kimball 2012</td>
<td>USA, Denmark, Netherlands, Germany</td>
<td>Multi-center, randomized, double-blind, placebo-controlled</td>
<td>154 HS patients with moderate to severe HS</td>
</tr>
<tr>
<td>Fadel 2014</td>
<td>Egypt</td>
<td>Single-center, randomized, controlled, split-body</td>
<td>10 HS patients (7F, 3M) 4 Hurley I, 4 Hurley II, 2 Hurley III</td>
</tr>
</tbody>
</table>

Abbreviations: ADA, adalimumab; bid, twice daily; BP, benzoyl peroxide; CL, clindamycin; CPA, cyproterone acetate; eow, every other week; ETA, etanercept; F, female; GC, gentamicin-collagen sponge; HS, hidradenitis suppurativa; IFX, infliximab; IPL, intense pulsed light; IV, intravenous;

DLQI scores reached statistical significance. More adverse events were observed in the adalimumab group, but this was not significant different from placebo. The study observed an overall pattern of disease evolution and speculated that the dosage used may had been suboptimal. A limitation of this study was that it was underpowered due to early termination of recruitment because of expiration of trial medication, and the fact that there was a difference of disease severity at baseline.

Subsequently, the optimal dosage was investigated by Kimball et al.11 in a three arm, well-conducted RCT in 154 patients. The study consisted of a double-blind phase.
<table>
<thead>
<tr>
<th>Intervention group(s)</th>
<th>Control group</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 topical CL 1% (dosing schedule unknown) for 12 weeks</td>
<td>14 PL for 12 weeks</td>
<td>Unjustifiable sample size, no intention-to-treat analysis</td>
</tr>
<tr>
<td>10 oral ethinylestradiol 50 µg/CPA 50mg (each menstrual cycle) for 12 months (with cross-over at 6 months)</td>
<td>8 oral ethinylestradiol 50 µg/ norgestrel 500 µg (each menstrual cycle) for 12 months (with cross-over at 6 months)</td>
<td>Unjustifiable sample size, no intention-to-treat analysis</td>
</tr>
<tr>
<td>16 (13F, 3M) oral TCN 500 mg bid plus topical PL, minimum of 3 months</td>
<td>18 (15F, 3M) topical CL 1% bid plus oral PL, minimum of 3 months</td>
<td>Unjustifiable sample size, no intention-to-treat analysis</td>
</tr>
<tr>
<td>124 (108F, 16M) surgical excision with PC plus GC</td>
<td>76 (72F, 4M) surgical excision with PC alone</td>
<td>No clear assessment of baseline severity</td>
</tr>
<tr>
<td>Nd:YAG laser monthly for 4 months plus BP wash 10% and CL 1% lotion</td>
<td>BP wash 10% and CL 1% lotion alone</td>
<td>No clear report on side effects</td>
</tr>
<tr>
<td>10 (6F, 4M), ETA SC 50 mg twice/week for 12 weeks</td>
<td>10 (7F, 3M), PL SC 50 mg twice/week for 12 weeks</td>
<td>Unjustifiable sample size</td>
</tr>
<tr>
<td>15 (12F, 3M) IFX (5 mg/kg) IV on weeks 0, 2, and 6</td>
<td>23 (14 F, 9 M) PL (5 mg/kg) IV on weeks 0, 2, and 6 (with cross-over at 8 weeks)</td>
<td>-</td>
</tr>
<tr>
<td>IPL twice/week for 4 weeks</td>
<td>No treatment</td>
<td>Unjustifiable sample size, no clear report on side effects</td>
</tr>
<tr>
<td>15 (12F, 3M) ADA SC 80 mg at baseline, 40 mg eow for 12 weeks</td>
<td>6 (5F, 1M) PL SC 80 mg at baseline, 40 mg eow for 12 weeks</td>
<td>Early termination of recruitment, difference in baseline severity</td>
</tr>
<tr>
<td>51 (36F, 15M) ADA SC 160mg week 0, 80mg week 2, 40mg weekly for 16 weeks 52 (38F, 14M) ADA SC 80mg week 0, 40 mg eow for 16 weeks</td>
<td>51 (36F, 15M) PL for 16 weeks</td>
<td>-</td>
</tr>
<tr>
<td>NMB gel plus IPL, twice monthly, maximum 6 months</td>
<td>Free NMB gel plus IPL, twice monthly, maximum of 6 months</td>
<td>Unjustifiable sample size</td>
</tr>
</tbody>
</table>

M, male; NMB, niosomal methylene blue; Nd:YAG, long-pulsed neodymium:yttrium-aluminium-garnet; PC, primary closure; PL, placebo; SC, subcutaneous; TCN, tetracycline.

and an open-label phase. Patients were assigned to adalimumab 40 mg every week (after 160 mg at week 0, and 80 mg at week 2), 40 mg every other week (after 80 mg at week 0), or placebo. At week 16 the proportion of patients achieving a PGA score of clear, minimal or mild, with at least two-grade improvement relative to baseline, was 17.6%, 9.6% and 3.9% for every week, every other week, and placebo, respectively. A significant difference was only seen in the every week group when compared to placebo (p=0.025), but not for patients randomly assigned to every other week (p=0.25). Significant improvements were also seen in secondary outcomes, including
### Table 4. Results of randomized controlled trials for the treatment of HS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Primary outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemmensen 1983(^14)</td>
<td>Cumulative score of patients’ assessment, number of abscesses, inflammatory nodules and pustules (monthly)</td>
<td>Clindamycin more effective after every monthly assessment (+311 vs -91 after 3 months)</td>
</tr>
<tr>
<td>Mortimer 1986(^15)</td>
<td>Cumulative score based on patients’ and observer assessment (12 months)</td>
<td>No difference</td>
</tr>
<tr>
<td>Jemec 1998(^16)</td>
<td>PaGA on VAS (monthly)</td>
<td>No difference</td>
</tr>
<tr>
<td>Buimer 2007(^17)</td>
<td>Percentage of postoperative complications, including dehiscence, infection and seroma (1 week)</td>
<td>Fewer complications for PC plus GC (35% vs 52%)</td>
</tr>
<tr>
<td>Mahmoud 2009(^18)</td>
<td>Modified HS-LASI, based on Sartorius score, percentage change from baseline (6 months)</td>
<td>More improvement on site treated with Nd:YAG (-72.7% vs -22.9%)</td>
</tr>
<tr>
<td>Adams 2010(^19)</td>
<td>PGA of clear or mild (12 weeks)</td>
<td>No difference</td>
</tr>
<tr>
<td>Grant 2010(^20)</td>
<td>HSSI &gt; 50% decrease from baseline, based on number of sites, body surface, number of lesions, drainage, pain VAS (8 weeks)</td>
<td>No difference</td>
</tr>
<tr>
<td>Highton 2011(^21)</td>
<td>Sartorius score, percentage change from baseline (12 months)</td>
<td>More improvement on the site treated with IPL (-33% vs +3%)</td>
</tr>
<tr>
<td>Miller 2011(^22)</td>
<td>Sartorius score, change from baseline (12 weeks)</td>
<td>No difference (-11.3 vs 5.8)</td>
</tr>
<tr>
<td>Kimball 2012(^23)</td>
<td>HS-PGA percentage patients achieving clear, minimal or mild (16 weeks)</td>
<td>Higher for ADA weekly (17.6% vs 3.9%), no difference for ADA eow (9.6% vs 3.9%)</td>
</tr>
<tr>
<td>Fadel 2014(^24)</td>
<td>Modified HS-LASI, based on Sartorius score, percentage reduction in lesion size (time of assessment unclear)</td>
<td>NMB gel produced a higher percentage reduction in lesion size (77.3% vs 44.1%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADA, adalimumab; AE, adverse event; CL, clindamycin; CPA, cyproterone acetate; CRP, C-reactive protein; DLQI, dermatology life quality index; ESR, erythrocyte sedimentation rate; eow, every other week; GC, gentamicin-collagen sponge; HS, hidradenitis suppurativa; HS-LASI, hidradenitis suppurativa lesion area and severity index; HSSI, hidradenitis suppurativa severity index; IFX, infliximab; IPL, intense pulsed light; NR, not reported; VAS, visual analog scale; WPAI-SHP, work productivity and activity impairment-specific health problem questionnaire.

VAS pain and DLQI for the every week group. A decrease in response was seen after the switch from every week to every other week in the open-label period. Kimball et al.\(^24\) also presented a thorough and structured safety analysis. For the phase 2 trial of adalimumab, numbers needed to treat (NNT) for the newly introduced outcome of HiSCR at week 16 was 4 (95% CI: 2.1-10.7), whereas numbers needed to harm (NNH)
### RCTs for the Treatment of HS

#### Table 4. Results of randomized controlled trials for the treatment of HS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Safety assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemmensen 1983</td>
<td>Cumulative score of patients’ assessment, number of abscesses, inflammatory nodules and pustules (monthly)</td>
<td>Clindamycin more effective after every monthly assessment (+311 vs -91 after 3 months)</td>
<td>p-Value: &lt;0.01, Secondary outcomes: None, Safety assessment: No side effects, except for local slight burning pain after application (2 CL, 3 PL)</td>
</tr>
<tr>
<td>Mortimer 1986</td>
<td>Cumulative score based on patients’ and observer assessment (12 months)</td>
<td>No difference</td>
<td>p-Value: NR, Secondary outcomes: PaGA on VAS, laboratory androgen assessment, CPA: 5 patients symptoms of weight gain, headaches and breast soreness Norgestrel: 8 patients with non specific side-effects</td>
</tr>
<tr>
<td>Jemec 1998</td>
<td>PaGA on VAS, soreness on VAS, counting of abscesses, counting of nodules</td>
<td>No difference</td>
<td>p-Value: NR, Secondary outcomes: PGA on VAS, soreness on VAS, counting of abscesses, counting of nodules, Safety assessment: Oral TCN: 2 patients with gastrointestinal upset, topical CL: 1 patient with suspected allergic reaction</td>
</tr>
<tr>
<td>Buimer 2007</td>
<td>Percentage of postoperative complications, including dehiscence, infection and seroma (1 week)</td>
<td>Fewer complications for PC plus GC (35% vs 52%)</td>
<td>p-Value: &lt;0.03, Secondary outcomes: NR, Safety assessment: Local recurrence rate, wound healing duration, percentage recovery in 2 months (assessed after 3 months)</td>
</tr>
<tr>
<td>Mahmoud 2009</td>
<td>Modified HS-LASI, based on Sartorius score, percentage change from baseline (6 months)</td>
<td>More improvement on site treated with Nd:YAG (-72.7% vs -22.9%)</td>
<td>p-Value: &lt;0.001, Secondary outcomes: Post-treatment questionnaire for patients, including pain, satisfaction, disease activity, and effectiveness. Histopathologic examination, Safety assessment: NR</td>
</tr>
<tr>
<td>Adams 2010</td>
<td>PGA of clear or mild (12 weeks)</td>
<td>No difference</td>
<td>p-Value: &gt;0.99, Secondary outcomes: PaGA, DLQI, patients’ pain scale, Safety assessment: Only mild injection site reactions, not specified for which group</td>
</tr>
<tr>
<td>Grant 2010</td>
<td>HSSI &gt; 50% decrease from baseline, based on number of sites, body surface, number of lesions, drainage, pain VAS (8 weeks)</td>
<td>No difference</td>
<td>p-Value: 0.092, Secondary outcomes: PGA, DLQI, VAS, laboratory markers (ESR and CRP), Safety assessment: More AEs in the PL group vs IFX, more serious AEs in the IFX group (pregnancy, hypertension) vs PL (infusion reaction)</td>
</tr>
<tr>
<td>Highton 2011</td>
<td>Sartorius score, percentage change from baseline (12 months)</td>
<td>More improvement on the site treated with IPL (-33% vs +3%)</td>
<td>p-Value: &lt;0.001, Secondary outcomes: Patients’ satisfaction on a Likert scale, Safety assessment: No complications</td>
</tr>
<tr>
<td>Miller 2011</td>
<td>Sartorius score, change from baseline (12 weeks)</td>
<td>No difference (-11.3 vs 5.8)</td>
<td>p-Value: 0.07, Secondary outcomes: Hurley score, VAS, DLQI, self-reported days with lesions, scoring by patient and physician, Safety assessment: More AEs in the ADA group vs PL group with regard to mild infections (p=0.06)</td>
</tr>
<tr>
<td>Kimball 2012</td>
<td>HS-PGA percentage patients achieving clear, minimal or mild (16 weeks)</td>
<td>Higher for ADA weekly (17.6% vs 3.9%), no difference for ADA every other week (9.6% vs 3.9%)</td>
<td>p-Value: 0.025 (weekly), 0.25 (eow), Secondary outcomes: Modified Sartorius score, Hurley score, VAS, DLQI, WPAI-SHP, PHQ-9, CRP, Safety assessment: 15 serious AEs during exposure to adalimumab</td>
</tr>
<tr>
<td>Fadel 2014</td>
<td>Modified HS-LASI, based on Sartorius score, percentage reduction in lesion size (time of assessment unclear)</td>
<td>NMB gel produced a higher percentage reduction in lesion size (77.3% vs 44.1%)</td>
<td>p-Value: &lt;0.01, Secondary outcomes: None, Safety assessment: None</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- ADA, adalimumab
- AE, adverse event
- CL, clindamycin
- CPA, cyproterone acetate
- CRP, C-reactive protein
- DLQI, dermatology life quality index
- ESR, erythrocyte sedimentation rate
- eow, every other week
- GC, gentamicin-collagen sponge
- HS, hidradenitis suppurativa
- HS-LASI, hidradenitis suppurativa lesion area and severity index
- HSSI, hidradenitis suppurativa severity index
- IFX, infliximab
- IPL, intense pulsed light
- NR, not reported
- Nd:YAG, long-pulsed neodymium:yttrium-aluminium-garnet
- NMB, niosomal methylene blue
- PaGA, patients’ global assessment
- PGA, physician global assessment
- PC, primary closure
- PHQ-9, patient health questionnaire-9
- PL, placebo
- TCN, tetracycline
- VAS, visual analog scale
- WPAI-SHP, work productivity and activity impairment-specific health problem questionnaire

For any serious adverse event was 26. This NNT to NNH ratio is quite favorable. This study concluded that adalimumab dosed every week alleviates moderate to severe HS, and therefore confirms the hypothesis of Miller et al. that a higher dosage is needed to obtain an optimal treatment efficacy.
**Antibiotics**

Two RCTs were found concerning the use of antibiotics for HS, and both included topical clindamycin.\textsuperscript{14,16} Clemmensen investigated the use of topical clindamycin 1\% solution versus placebo in a double blind, placebo controlled trial in 30 patients.\textsuperscript{14} A significant difference in a non-validated, cumulative score, based on patient assessment, number of abscesses, inflammatory nodules and pustules, was found after each monthly evaluation. A positive difference in score indicated improvement. After 3 months the difference in cumulative score was +311 for the clindamycin group and –91 for the placebo group (p<0.01). When each parameter was evaluated separately, clindamycin was not superior in case of inflammatory nodules and abscesses. This was probably due to the initial sparse number of lesions. No side effects were observed, except for a local slight burning pain after application in five cases, of which three patients received placebo. Limitations of the study included an unjustifiable sample size and the fact that there was no intention-to-treat analysis.

Jemec and Wendelboe compared topical clindamycin 1\% solution twice daily with oral tetracycline 500 mg twice daily in 46 patients for a minimum of 3 months in a double-blind, double dummy trial.\textsuperscript{16} Patients in both groups showed improvement from baseline, but no significant difference in efficacy between the two treatments was found. Patients’ global assessment was significantly worse than physician’s assessment, and they found that soreness was the key factor in patients’ overall assessment of disease. Therefore they concluded that soreness, and other subjective factors should be included as an outcome variable in future therapy studies. An increased consensus between patients’ and physicians’ assessment was observed later on in the study. No information was provided on side effects, except for two patients who discontinued the study due to gastrointestinal upset and one patient with a suspected allergic reaction to topical clindamycin. All over there was a high drop-out rate, with twice as much drop-outs in the systemic treatment group. Comparable to the study of Clemmensen, there was an unjustifiable sample size and no intention-to-treat analysis.

**Hormones**

Mortimer et al.\textsuperscript{24} allocated 24 patients in two groups matched for age and disease duration, and compared oral ethinylestradiol 50 µg / cyproterone acetate 50 mg with ethinylestradiol 50 µg / norgestrel 500 µg. The treatment was given sequentially for 12 months with cross-over at 6 months. Both treatment arms improved compared to baseline, and there was no significant difference between the two groups. There was a high drop-out rate. Side effects were mostly non specific in case of norgestrel, but cyproterone acetate seemed to cause weight gain, headaches and breast soreness. Based on the results that seven patients cleared, five improved, four remained unchanged and two deteriorated, the authors concluded that anti-androgen therapy appears to be beneficial in the treatment of HS. The study was limited due to unjustifiable sample size and no intention-to-treat analysis.
Surgery

In case of surgical procedures for HS there is a lack of RCTs. Buimer et al.\textsuperscript{17} conducted a non-blinded randomized study to investigate whether enclosure of antibiotics after primary excision and closure reduces the number of postoperative complications. A total of 200 patients was included, of which 76 patients were treated with excision and primary closure only, and 124 patients received an additional 5 x 5 cm gentamicin-collagen sponge after surgery. Overall, 59% of the patients treated with gentamicin had no complications, like dehiscence and infection, after 1 week, versus 47% in the group without antibiotics (p<0.03). However, this significant difference was not seen after 3 months. Also gentamicin had no significant influence on the local recurrence rate and the duration of wound healing. Side effects of gentamicin were not reported. Also no clear assessment of baseline severity was available. The baseline randomization imbalance was due to early cessation of the study. Although the beneficial effect of gentamicin does not influence the long-term prognosis of HS, the authors recommend the usage of gentamicin after excision.

Laser

Three studies assessed the efficacy of laser treatment, including one study on Nd:YAG laser treatment and two studies concerning the intense pulsed light (IPL).\textsuperscript{18,21,23} Mahmoud et al.\textsuperscript{18} conducted a randomized, right-left within-patient controlled trial in 22 patients. Patients were treated monthly for four months with the Nd:YAG laser and topical treatment consisting of clindamycin 1% lotion and benzoyl peroxide 10% wash. The same topical treatment was applied on the control side of the body. To assess efficacy, a modified scoring system based on Sartorius score, with additional patients’ symptoms, including erythema, edema, pain, and discharge, was used. The percent decrease of severity form baseline, indicating improvement, after 6 months was -72.7% on the laser treated side, and -22.9% on the control side (p<0.001). The treatment was associated with minimal patient discomfort, and 60% of the patients did not experience pain related to laser treatment. There was no clear report on side effects. The suggested mechanism of action of the Nd:YAG laser is destruction of the follicular unit.

Highton et al.\textsuperscript{21} investigated 18 patients in a within-patient study to determine whether IPL is an effective treatment for HS. One side of the body was treated with IPL, twice a week, for 4 weeks. The contralateral side received no treatment. A significant improvement was seen in Sartorius score averaged for all treated sites when compared to baseline that was maintained at 12 months (-33% vs +3%, p<0.001). There was a possible trend towards recurrence at 12 months.

Fadel and Tawfik treated 10 patients in a randomized split-body study to evaluate the efficacy of methylene blue (MB) as a photosensitizer delivered as a niosomal gel and activated by IPL (630 nm).\textsuperscript{23} One side of the body was treated with niosomal MB gel and the other side with free MB gel. Patients were treated twice a month, for a maximum of
RCTS FOR THE TREATMENT OF HS

6 months. The follow-up period was up to 6 months after the last treatment. Treatment efficacy was based on the Sartorius score. A significant difference in reduction of lesions was found: 77.3% for the niosomal MB gel side and 44.1% for the free MB gel side (p<0.01). The authors conclude that the use of niosomal gel as a delivery system for MB provides a better penetration to the deeper layers of the dermis. No side-effects occurred.

RANDOMIZED CONTROLLED TRIALS RECENTLY COMPLETED AND ONGOING

Several randomized controlled trials have been recently completed or are registered as ongoing and results are awaited to be made public. 

**Biologics**

PIONEER I and II, two phase 3, double-blind, randomized, placebo-controlled trials to assess the efficacy and safety of adalimumab, were recently completed. Results have already been partially presented in congresses, and these preliminary reports support the validity of the phase 2 trial reported by Kimball et al. Furthermore, an ongoing randomized, double-blind, controlled trial is registered in order to study the efficacy and safety of anakinra, a human IL-1 receptor antagonist, 100 mg daily for 12 weeks compared to placebo, for the treatment of Hurley stage II and III HS. A phase IIa randomized, double-blind, placebo-controlled, multicenter study to assess the safety, tolerability and preliminary efficacy of MEDI8968, a blocking antibody to IL-1RI, in patients with moderate to severe HS is registered, with active treatment being given as subcutaneous injection at baseline, week 4 and week 8.

**Other treatments**

A prospective, randomized, controlled clinical trial comparing the efficacy of carbon dioxide laser excision to surgical deroofing in the treatment of HS is registered. A randomized controlled, single-blind trial comparing efficacy of antibiotic therapy (clindamycin 300 mg twice daily and rifampin 300 mg twice daily for 10 weeks) alone to antibiotic therapy (clindamycin 300 mg twice daily and rifampin 300 mg twice daily for 2 weeks) plus 3 Nd:Yag laser sessions is also registered. Lastly, a prospective multi-center blinded, randomized, controlled clinical trial comparing the efficacy of povodine topical cream twice daily to 10% benzoylperoxide topical body wash twice daily for the treatment of HS is currently being conducted.

CONCLUSIONS AND RECOMMENDATIONS

This systematic review emphasizes the need for the use of validated and uniform outcomes, in order to facilitate indirect comparison of available treatments and to promote evidence based clinical practice. HiSCR is a validated outcome which
is highly recommended to be used in the future as primary outcome for assessing the efficacy of anti-inflammatory treatments. Future studies should also include a justifiable sample size, with the use of HiSCR, and a thorough report of side effects, both physician and patient rated (pain, tolerability).

Since HS is a chronic debilitating disease which leads to low quality of life, working disability, pain and is associated with a higher rate of several cardiovascular disease risk factors, future clinical trials should include patient rated outcomes, especially regarding quality of life, working ability, pain scores and patient satisfaction. The assessment of the possible effect of various treatments in cardiovascular disease risk factors is also interesting.

Combination of the various available treatment modalities, especially combination of surgical approaches with anti-inflammatory treatments (Fig. 4), is important. Results from Mahmoud et al. provide initial evidence that such a combination can have a positive effect. Adjuvant therapy with topical (clindamycin) or systemic antibiotics and/or TNF inhibitors prior to surgery may lead to less invasive surgery and better short and long term outcomes in Hurley II and III stages HS. This is an interesting hypothesis that warrants further investigation.

Regarding biologics, further evaluation of etanercept is not recommended. Infliximab shows evidence of efficacy, and a possible future clinical trial, with appropriate design and use of validated outcomes may yield significant results.

HS can be seen in prepubertal age, with only 2% of cases occurring before the age of 11 years. Data regarding HS in children and adolescents are scarce. So far, recommendations for treating children are based on clinical case reports and extrapolation of the results in adult populations. Randomized multicenter clinical trials with adequate sample sizes are needed to provide high quality evidence in this specific age group.

The balance between desirable and undesirable outcomes of alternative treatment strategies (the benefit-risk ratio, preferably analyzed with a structured approach) is becoming more and more important, both for treating physicians and for authorities during drug regulatory decision-making. Future studies should facilitate such assessments. Most of
the trials included in this review lack a medium- and long-term assessment of the efficacy and safety of the studied treatments; future studies should include these assessments.

Implications for daily clinical practice
This systematic review provides evidence that can be used to promote evidence based daily clinical practice. For Hurley stage I and mild not widespread Hurley II, topical clindamycin 1% solution/gel b.i.d. for 12 weeks is recommended. Tetracycline 500 p.o. b.i.d. for 4 months is recommended for more widespread disease. If a patient fails to respond, adalimumab 160 mg subcutaneously at week 0, 80 mg at week 2; then 40 mg weekly, or infliximab (5 mg/kg) IV on weeks 0, 2, and 6 and then every 8 weeks can be considered for moderate to severe disease. Hormonal therapy can be considered for moderate to severe disease, especially in females with endocrinological comorbidities, but the balance between benefits and possible side effects of long-term treatment has to be carefully evaluated. IPL for Hurley II and III stages is also an evidence based treatment and the use of niosomal methylene blue seems to enhance efficacy. For these stages, Nd:YAG laser monthly for 4 months combined with topical anti-inflammatory treatments seems to be a therapeutic option. After surgical excision, addition of local treatments like a gentamicin-collagen sponge has been shown to result in fewer complications and is a rational decision.

Integrating results of RCTs in the current state of the art treatment of hidradenitis suppurativa
It should be noted that this review focused on RCTs only. Hence, several established treatment options are not discussed. According to most experts, the mainstay of treatment in HS is surgical intervention in an early stage of disease, but RCTs on surgical interventions are lacking, probably because it is considered unethical to deny the control group access to surgical treatment for a prolonged period of time. The results of surgery are usually described in prospective or retrospective cohort studies with the percentage of successfully removed lesions as primary outcome. Besides tetracycline, there are other antibiotics that may be even more effective in HS, e.g. the combination of clindamycin and rifampicin, or clindamycin as monotherapy, but they were not investigated in RCTs. Most of the recently performed RCTs investigate biologics, and some of these studies are of high quality because they are designed for registration purposes. Anti-inflammatory agents reduce inflammation, pain, swelling, and purulent discharge, but epithelialized cavities and fistulas will not disappear. In daily practice, the new anti-inflammatory agents are used in combination with other treatment options as illustrated in Fig. 4. Some patients can be cured with surgery only, some with antibiotics only, and the severe cases may require all treatment modalities including anti-inflammatory agents.
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CHAPTER 3

Hidradenitis suppurativa not associated with CARD15/NOD2 mutation: a case series

D.C. van Rappard, J.R. Mekkes

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Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease characterized by painful abscesses, scars, and sinus tract formation. Typically affected are the axilla, groin, and anogenital region. Its prevalence has been estimated to be 1-4% with a female predominance. Its pathogenesis consists of follicular plugging followed by gland rupture and abscess formation. Its aetiology is still poorly understood. HS is strongly associated with smoking and obesity, and there is a familial factor in up to 30% of patients.1

Fitzsimmons et al.2 systematically investigated the genetic basis of HS in 26 families and observed an autosomal dominant inheritance pattern. More recently mutations in 3 genes (PSEN1, PSENEN, NCSTN) encoding for γ-secretase, which may play a role in the etiology of HS, were identified in six Chinese families.3 γ-secretase cleaves type 1 transmembrane proteins, including amyloid precursor protein and Notch. Genetic inactivation of γ-secretase in mouse skin produces follicular plugging, which is histopathologically similar to follicular plugging observed in human HS.

Another hypothesis is that polymorphisms in the CARD15/NOD2 gene, as expressed in Blau’s syndrome and Crohn’s disease, may play a comparable role in HS. Blau’s syndrome is a rare autosomal dominant granulomatous disease, characterized by arthritis with camptodactyly, uveitis, and intermittent skin eruptions. The CARD15/
The NOD2 gene is part of the ancestral innate immune system that senses and eliminates bacteria and is involved in apoptosis regulation. It is predominantly expressed in monocytes, a cell type that can differentiate into giant and epithelioid cells aggregating in granuloma formations. Tissues of patients with Blau’s syndrome were tested positive for *Mycobacterium avium* ss. paratuberculosis, which is an intracellular organism that causes enteric granulomas in Crohn’s disease.

Blau’s syndrome, together with Crohn’s disease and early onset sarcoidosis are confirmed associations with CARD15/NOD2 mutations. Currently research is ongoing in several fields where a genetic susceptibility factor is suspected. Nassar et al. analysed 10 patients with HS and found only one to be heterozygous for the R702W polymorphism, concluding no association between CARD15/NOD2 and HS.

Nevertheless, several observations support the suspicion of an association between CARD15/NOD2 mutations and HS. First of all, HS is strongly associated with Crohn’s disease, and in approximately 40% of Crohn’s disease patients, this mutation can be demonstrated. In addition, both diseases are characterized by an uncontrolled inflammatory response driven by tumor necrosis factor-α (TNF-α) with a prominent granulomatous histology, and in both diseases pyoderma gangrenosum may develop. Granuloma formation is also a feature of Blau’s syndrome, and these patients may have papular or plaque-like skin eruptions and pyoderma gangrenosum. We hypothesized that there might be a subgroup within the HS patients with R702W polymorphism and decided to analyze the entire coding region of the CARD15/NOD2 gene in six patients with a high “pre-test probability” of having a genetic factor, separated in three categories: (i) two patients (one male, one female) with HS and coexisting pyoderma gangrenosum (Fig. 1); (ii) two female patients with HS, coexisting pyoderma gangrenosum and additional (cutaneous) Crohn’s disease; and (iii) two young female patients with a pre-pubertal onset of HS and a positive family history of severe HS.

DNA was isolated from peripheral blood lymphocytes of the six patients. Exon-specific M13-tagged primers were used to amplify all coding exons including flanking regions of the NOD2 gene (RefSeq NM_022162.1). Primer sequences are available upon request. Each exon was amplified and sequenced on both strands using BigDye Terminator Version 1.1 (Applied Biosystems, Nieuwekerk a/d IJssel, the Netherlands) cycle sequencing.

In none of the six patients could a mutation of the CARD15/NOD2 be detected. As their high-risk profile indicated that these patients were strongly suspected to express the CARD15/NOD2 mutation, it seems unlikely that this mutation will be found in other patients with HS. Therefore, our results confirm the earlier observation that HS is probably not associated with CARD15/NOD2 mutations. However, a larger cohort is necessary to strengthen this conclusion.
REFERENCES


CHAPTER 4

Four cases of plaque form hidradenitis suppurativa

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic skin disease characterized by painful nodules, abscesses, sinuses, and scarring, usually in the inverse areas of the body, such as the axilla, groin, submammary and perianal areas. The exact cause is unknown, but plugging of the hair follicle plays a role. An association with smoking and metabolic syndrome has been suggested.\(^1\) It may occur in atypical locations such as the retroauricular folds, face, neck, waist, hip, back, thighs and periumbilical region.\(^2,3\) Canoui-Poitrine et al.\(^4\) identified three HS phenotypes, called ‘axillary-mammary’, ‘follicular’, and ‘gluteal’.

In a cohort of 596 HS-patients, we noticed that four patients had an atypical clinical presentation, consisting of large superficial slowly migrating inflammatory plaques on different parts of the body.

CASE SERIES

Patient 1 is a 54-year-old male smoker with severe HS in his axillae, groins and perianal area since 20 years. Strikingly, he developed a 15x7 cm large purple plaque on his abdomen, with a central cribriform scar surrounded by a slowly migrating active border with purulent fistulas (Fig. 1a,b). No histopathology was obtained. He was successfully treated with clindamycin and rifampicin, together with primary excisions for his typical HS lesions and deroofing of his abdominal plaque. The plaque did not expand beyond the borders of surgery (Fig. 1c,d).

Patient 2 is a 60-year-old female smoker, with a 25-year history of HS of the groins, perineum and axillae. Recently, a superficial suppurative purple plaque with active border developed on her right arm (Fig. 2a). The plaque slowly expanded over time, leaving cribriform central scarring behind (Fig. 2b). The lesion was successfully treated with oral clindamycin, topical betamethasonedipropionate, and deroofing (Fig. 2c). Histopathology confirmed the diagnosis HS (Fig. 2d,e).

Patient 3 is a 30-year-old female former smoker, with acne conglobata and HS of the pubic and perianal areas since 5 years. For two years, a persistent dark purple 10x10 cm cribriform plaque with multiple fistulas with purulent discharge had been present on her leg (Fig. 3a). A biopsy revealed the diagnosis of HS (Fig. 3c). Treatment with consecutive prednisone 30 mg, clindamycin, and 5 infusions of infliximab eventually led to disease control, without surgical intervention (Fig. 3b).

Patient 4 is a 50-year-old male former smoker, suffering from invalidating HS of the scrotal and perianal area since 20 years. Subsequently, he also presented with large 20x20 cm erythematous plaques with epithelial bridging, suppurative discharge and pigmented borders on his thighs, earlier diagnosed as pyoderma gangrenosum (PG) (Fig. 4a). However, histopathology was compatible with the diagnosis of HS (Fig. 4b). He was treated with multiple anti-inflammatory therapies including antibiotics and biologicals, in combination with surgical interventions, resulting in a well-controlled disease.
Figure 1. Patient 1. (a,b) A large purple plaque on the lower abdomen, consisting of superficial purulent fistulas in a cribriform pattern surrounded by an active border. (c,d) End stage of disease, after treatment with clindamycin, rifampicin and a deroofing procedure. The entire dermis is destroyed, including all hair follicles.

Figure 2. Patient 2. (a) A suppurative, superficial purple plaque with active border on the inner side of the right arm. (b) The plaque slowly expanded leaving a trail of cribriform central scarring behind. (c) The active border after treatment with a deroofing procedure. (d) Low power view of skin excision: intact epidermis overlying epithelialized sinus tracts surrounded by dense inflammation. Necrosis is absent. HE stain, x25. (e) Detail of squamous epithelium island in the deep dermis, surrounded and infiltrated by inflammatory cells (neutrophils, lymphocytes and histiocytes). HE stain, x200.
Figure 3. Patient 3. (a) A dark purple cribriform plaque on the back of the upper right leg, consisting of multiple fistulas with purulent discharge. (b) After treatment with prednisone, clindamycin and 5 infusions of infliximab. (c) Histopathology: detail of dermis showing fibrosis, hemorrhage, inflammation and benign epithelial proliferations. HE stain, x100.

Figure 4. Patient 4. (a) Large erythematous plaques with epithelial bridging, suppurative discharge and pigmented borders on the upper thighs. The inflammatory process slowly migrates and leaves a deep scar. (b) Histopathology: low power view of skin excision showing sinus tracts containing keratin, surrounded by inflammatory infiltrates of lymphocytes and plasma cells. HE stain, x25.
DISCUSSION

We describe four patients in a cohort of 596 HS-patients with a distinct atypical plaque forming type of HS. All patients presented with purple inflamed plaques on different parts of the body, with some resemblance to PG.

PG is a rare inflammatory skin disease in which progressive ulcers with raised undermined violaceous borders develop anywhere on the body, most commonly on the legs. PG may occur in combination with HS, but the plaques in our patients were different from PG: ulceration was absent and all lesions expressed a strikingly cribriform pattern.

These clinically very typical cribriform plaques have been described by other authors before, but under different names, which is very confusing. Two authors described patients with identical lesions but they called it pyoderma gangrenosum and used the acronym PASH syndrome (PG, acne, and HS). Vilar-Alejo et al. described a 47-year-old patient with cribriform plaques identical to patient 4, but named it pyoderma vegetans (PV), based on the histopathological finding of pseudoepitheliomatous hyperplasia. PV is a very rare disease in immune compromised patients, characterized by ulcerations and verrucous plaques.

The plaques in our patients were not verrucous, but rather suppurative, with multiple superficial fistulas as seen in HS. We hypothesized that these plaques are neither PV nor PG, but may be an atypical clinical variant of HS.

In three of our patients histopathology was available. All specimens showed a similar pattern of irregularly shaped epidermal surfaces with keratotic plugging, dilatation of follicles, sinuses lined by stratified squamous epithelium, and formation of microabscesses. An infiltrate consisting of lymphocytes, histiocytes and many plasma cells was present. Granulation tissue and areas of fibrosis indicated a longstanding inflammatory process.

PG and HS can be histologically hard to distinguish, as they are both characterized by neutrophilic inflammation. Pathognomonic characteristics for PG like ulceration, necrosis and secondary vasculitis were absent in our patients. The histology was also not compatible with PV. Pseudoepitheliomatous hyperplasia, induced by chronic inflammation, can be present in both PV and HS.

For these reasons we would like to propose a new clinical entity that has not been described in the literature before: plaque form HS. This HS form is a rare variant of HS that may occur on any part of the body. It starts as an inflammatory infiltrate localized around hair follicles. Clinically, multiple pustules and abscesses form expanding purple plaques. In the end stage of the disease the entire dermis including all hair follicles is destroyed. Ulceration does not occur.

Due to the rarity of the disease, a recommendation for treatment can only be based on our own limited experience. The patients responded well to anti-inflammatory medication and surgery (deroofing). No Koebner phenomenon was observed. More similar observations are needed to confirm this clinical entity and its treatment.
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Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic relapsing skin disease. Recent studies have shown promising results of anti-tumor necrosis factor-alpha treatment.

Objective: To compare the efficacy and safety of infliximab and adalimumab in the treatment of HS.

Methods: A retrospective study was performed to compare 2 cohorts of 10 adult patients suffering from severe, recalcitrant HS. In 2005, 10 patients were treated with infliximab intravenous (i.v.) (3 infusions of 5 mg/kg at weeks 0, 2, and 6). In 2009, 10 other patients were treated in the same hospital with adalimumab subcutaneous (s.c.) 40 mg every other week. Both cohorts were followed up for 1 year using identical evaluation methods [Sartorius score, quality of life index, reduction of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), patient and doctor global assessment, and duration of efficacy].

Results: Nineteen patients completed the study. In both groups, the severity of the HS diminished. Infliximab performed better in all aspects. The average Sartorius score was reduced to 54% of baseline for the infliximab group and 66% of baseline for the adalimumab group.

Conclusions: Adalimumab s.c. 40 mg every other week is less effective than infliximab i.v. 5 mg/kg at weeks 0, 2, and 6.
INTRODUCTION

Hidradenitis suppurativa (HS), also called acne inversa or ectopica, is a chronic relapsing skin disease. It is characterized by purulent inflammation of occluded hair follicles and sebaceous glands, leading to abscesses, scars, and sinus tract formation. Typically affected are the apocrine gland-bearing areas such as axilla, groin, and perineum. Due to the invariably painful, unsightly, odorous lesions, HS is a distressing condition for many patients and is associated with a significant impairment of quality of life, both as a physical ailment and social concern. Current treatment modalities, like antibiotics, corticosteroids, antiandrogens, retinoids, dapsone, and cyclosporine, have failed to provide a consistently effective treatment strategy. In case of severe HS, radical surgical excision of affected sites is considered the most efficient therapy.

Recent studies have shown promising results of anti-tumor necrosis factor-alpha (TNF-α) biologic agents in patients with severe HS. These agents have demonstrated efficacy in other chronic inflammatory disorders such as Crohn’s disease, psoriasis, and rheumatoid arthritis. Since the first observation of the beneficial effect of infliximab in patients with Crohn’s disease and coexisting HS, several TNF-α inhibitors have been evaluated in HS patients.

In 2009, Haslund et al. performed a systematic search to evaluate the three TNF-α inhibitors, infliximab, etanercept, and adalimumab. A total of 34 publications, describing treatment for 105 patients, were retrieved. No randomized controlled trials were available yet. A positive treatment outcome was reported in 45/52 infliximab patients, 35/37 etanercept patients, and 16/16 adalimumab patients. In addition, results from more recent articles confirm the activity of infliximab, partly confirm the activity of adalimumab, and discourage the use of etanercept.

This report describes our experiences with the two most suitable biologic agents for the treatment of HS: infliximab and adalimumab. In 2005, 10 patients were treated with infliximab intravenous (i.v.) according to the dosing schedule for Crohn’s disease (5 mg/kg at weeks 0, 2, and 6). In 2009, 10 patients were treated with adalimumab subcutaneous (s.c.) 40 mg every other week. Both patient groups were treated in the same hospital and evaluated in exactly the same way, which made it possible, with restrictions, to compare the two TNF-α inhibitors.

PATIENTS AND METHODS

In this retrospective study, 2 cohorts of 10 adult patients suffering from severe, recalcitrant HS were compared. The first cohort was treated with infliximab and the second cohort was treated with adalimumab.

In 2005, 10 patients were treated with infliximab i.v. (3 infusions of 5 mg/kg at weeks 0, 2, and 6) and followed up for at least 1 year. The disease activity before and after treatment was evaluated using the acne skin score as described by Sartorius
et al.\textsuperscript{15} in 2003. The “Sartorius score”, which was recently simplified, is a validated tool for assessing disease severity in HS patients, with a low interobserver variability.\textsuperscript{16,17}

In addition, the patients were asked to give an overall judgment of the effectiveness of infliximab after 1 year, on a 10-point scale (1 = no improvement to 10 = excellent result). Also a doctor global assessment was performed after 1 year using a 4-point scale (1 = no improvement, 2 = moderately improved, 3 = improved and 4 = free of lesions). Quality of life measurements were performed before treatment and after 1 year using the Dermatology Quality of Life Index (DQLI), a validated score with a maximum of 30 points, which correlates with a severe impact on quality of life.\textsuperscript{18}

The clinical efficacy was further documented by means of clinical photography and objective parameters like the erythrocyte sedimentation rate (ESR in mm/h) and C-reactive protein (CRP in mg/L).

In 2009, 10 other patients were treated in the same hospital with adalimumab s.c. 40 mg every other week and were also subsequently followed up for 1 year. One of the patients was not able to complete the study due to psychological problems and was considered as “drop out” after 2 months. In the nine remaining patients, disease activity was evaluated using the exact same measurements and tools as used in the infliximab group 4 years earlier.

**RESULTS**

Ten patients treated with infliximab (six females, four males, average age 41, average disease duration 18.5 years, and average Sartorius score 164) and nine patients treated with adalimumab (one female, eight males, average age 48, average disease duration 19 years, and average Sartorius score 170) completed the study. The patient characteristics and results are summarized in Table 1. In both groups, the severity of the HS diminished (Fig. 1 and 2).

In the infliximab group, the average Sartorius score was 164 ± 50 (mean ± SD) before treatment and diminished to 89 ± 49 after 1 year (p = 0.002). In the adalimumab group, the average Sartorius score was 170 ± 48 before treatment and diminished to 113 ± 73 after 1 year (p = 0.02). These results represent a significant reduction in both groups and correlate with a reduction to 54% of baseline for the infliximab group and 66% of baseline for the adalimumab group (Fig. 3A).

In both the infliximab and the adalimumab groups, initially a rapid and significant reduction of the inflammatory laboratory parameters ESR and CRP was observed. After 1 year, only the reduction of the infliximab group remained significant. In the infliximab group, the mean ESR was reduced from 31.8 before treatment to 11.5 after 2 months (p = 0.02). After 1 year, the mean ESR was 14.5 (p = 0.05). CRP was reduced from 31.7 to 5.5 after 2 months (p = 0.015), and 8.9 after 1 year (p = 0.03).

In the adalimumab group, the mean ESR was reduced from 36.2 before treatment to 19.4 after 2 months (p = 0.05). After 1 year, the mean ESR was 33.9 (p = 0.8). CRP
was reduced from 22.5 to 11 after 2 months ($p = 0.04$), and increased to 24.6 after 1 year ($p = 0.7$) (Fig. 3B).

Quality of life was measured using the DQLI. As could be expected, the quality of life before treatment was not good in both groups. In the infliximab group, the mean score was $18.4 \pm 7.9$ (mean $\pm$ SD) before treatment and improved to $9.3 \pm 9.1$ ($p = 0.007$) after 1 year. In the adalimumab group, the mean score before treatment was $13.3 \pm 7.1$ and after 1 year a small, but no significant improvement was observed ($11.7 \pm 9.9$, $p = 0.66$) (Fig. 3C).

Both patient groups rated the efficacy of their treatment on a 10-point scale. In the infliximab group, the mean score after 1 year was $7.9 \pm 2$ (mean $\pm$ SD). In the adalimumab group, the mean score after 1 year was $5.1 \pm 2.8$ (Fig. 3D).

In addition, a doctor global assessment of disease improvement was performed after 1 year using a 4-point scale. In the infliximab group, three patients were “free of lesions”, six patients were “improved” and one patient was rated as “moderately improved”, resulting in a mean score of $3.2 \pm 0.6$ (mean $\pm$ SD). In the adalimumab group, four patients were “improved”, three patients were “moderately improved” and two patients were rated as “no improvement”, resulting in a lower mean score ($2.2 \pm 0.8$) compared with the infliximab group (Fig. 3D).

There were no serious adverse events. One of the patients treated with infliximab developed an acute arthritis and myalgia, which was probably related to treatment. The arthritis was treated with non-steroidal anti-inflammatory drugs and a short course of prednisone and disappeared completely. In the adalimumab group, three patients

### Table 1. Summary of patient characteristics and results

<table>
<thead>
<tr>
<th></th>
<th>infliximab (n=10)</th>
<th>adalimumab (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>48</td>
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<td>1</td>
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<tr>
<td>Smoker</td>
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<td>8</td>
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<td>Duration disease (years)</td>
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<td>19</td>
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<tr>
<td>Sartorius score before treatment</td>
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<td>170</td>
</tr>
<tr>
<td>Sartorius score after 1 year</td>
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<td>113</td>
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<tr>
<td>DLQI before treatment</td>
<td>18.4</td>
<td>13.3</td>
</tr>
<tr>
<td>DLQI after 1 year</td>
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<td>11.7</td>
</tr>
<tr>
<td>CRP before treatment (mg/L)</td>
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<td>22.5</td>
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<tr>
<td>CRP after 1 year (mg/L)</td>
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<td>24.6</td>
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<tr>
<td>ESR before treatment (mm/h)</td>
<td>31.8</td>
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</tr>
<tr>
<td>ESR after 1 year (mm/h)</td>
<td>14.5</td>
<td>33.9</td>
</tr>
</tbody>
</table>

Abbreviations: DQLI = Dermatology Quality of Life Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
complained of fatigue, directly after treatment. One of the patients complained of a painful skin injection site due to the repeated injections.

**DISCUSSION**

The conclusion from this small cohort study is that both treatments are effective but that adalimumab s.c. 40 mg every other week is less effective than infliximab i.v. 5 mg/kg at weeks 0, 2, and 6. Infliximab performed better in all aspects (Sartorius score, quality of life, reduction of ESR and CRP, patient and doctor global assessment, and duration of efficacy). The quality of life improved significantly in the infliximab group, while in the adalimumab group only a minor and insignificant change was observed. Both groups showed improvement in the first several months as reflected in the laboratory results. However, when evaluating both groups after 1 year, the majority of patients, especially in the adalimumab group, showed recurrence. Recurrence could have been expected in the infliximab group, where only three infusions had been administered, followed by an observation period, but not in the adalimumab group where continuous treatment every other week was given.

The intention of the study was to compare 2 equal groups, both consisting of 10 patients. Unfortunately, one of the patients of the adalimumab group was not able
to complete the study; he chose to discontinue the treatment due to psychological problems. This was not considered as an adverse effect of treatment, because the patient was familiar with this ailment previously.

Of the remaining 19 patients who completed the study, 18 smoked or had been smoking in the past. This is not surprising, because 80–95% of the HS population in the Netherlands is smoking, and smoking appears to be an important risk factor for HS. There is a direct correlation between disease severity and tobacco intake.

The patient groups were comparable in age, severity, and disease duration. There was an unexpected predominance of male subjects in the adalimumab group; normally women are more commonly affected with HS than men.

Our study has certain limitations that should be taken into account. First of all, a prospective randomized controlled design would have been preferred to compare the two treatment modalities. Instead, we describe a retrospective study, and therefore conclusions may not be very strong. Another restriction to our cohort study is that both groups were not treated and evaluated at the same time. Despite this drawback of comparing two historical cohorts, we think that the conclusion is valid, because the clinical setting and all evaluation methods were identical. Objective criteria such as ESR and CRP were used, and validated scoring methods such as the DQLI and the Sartorius score.

The conclusion is in accordance with the general consensus that is now arising from the literature, namely that infliximab is the most effective biological in HS, followed
INFLIXIMAB AND ADALIMUMAB IN HS

Figure 3. (A) Sartorius score, mean ± SD. The Sartorius score diminished during treatment with adalimumab (upper line, \( p = 0.02 \)) and infliximab (lower line, \( p = 0.002 \)). (B) Erythrocyte sedimentation rate (ESR in mm/h) and C-reactive protein (CRP in mg/L) during treatment. CRP and ESR are significantly reduced 2 months after treatment with infliximab or adalimumab. After 1 year, the CRP and ESR reduction is still significant in the infliximab group. (C) Dermatology Quality of Life Index (DQLI), mean ± SD, before and after treatment with infliximab (significant improvement, \( p = 0.007 \)) and before and after treatment with adalimumab 40 mg every other week (difference not significant). (D) Patient and doctor global assessment of the efficacy of infliximab versus adalimumab, mean ± SD. The patient rated the efficacy of treatment on a 10-point scale. The doctor scored improvement on a 4-point scale (1 = no improvement, 2 = moderately improved, 3 = improved, and 4 = free of lesions).

by adalimumab, probably in a higher dose (40 mg weekly), and that the efficacy of etanercept is still controversial.

After Haslun et al. published a review in 2009 concluding the efficacy of infliximab, etanercept, and adalimumab, a few additional relevant articles appeared, including randomized controlled trials.

Grant et al. confirmed the efficacy of infliximab in a randomized, double-blind, placebo-controlled trial with 38 patients who received either infliximab i.v. (5 mg/kg at weeks 0, 2, and 6 and subsequently every 2 months) or placebo. A superiority of infliximab was demonstrated. Subsequently, a case series of four patients with recalcitrant HS revealed marked improvement on the HS lesions for all four participants after three infliximab infusions.

In case of etanercept, the recent literature is not supportive for its efficacy in the treatment of HS. A recently published randomized, double-blind, placebo-controlled
study with 20 patients, concluded that etanercept, administered twice weekly (50 mg s.c.),
did not have significant efficacy in the improvement of HS.\textsuperscript{13} As a consequence of these
results, the off-label use of etanercept in HS has been discouraged by the manufacturer.

The latest studies on adalimumab published in 2010 drew adverse conclusions. Amano et al.\textsuperscript{11} reported 10 patients treated with adalimumab s.c. in doses of 160 mg
at week 0, followed by 80 mg at week 1, and 40 mg at alternate weeks. No statistically
clinical improvement was observed. Another recent study by Arenbergerova et al.\textsuperscript{12}
concluded that treatment with adalimumab s.c., initial dosage 80 and 40 mg at alternate
weeks was a suitable long-term treatment for the eight participating HS patients.

A similarity can be recognized when comparing the efficacy of TNF-\(\alpha\) inhibitors in
patients with HS to their efficacy in patients with Crohn's disease. Patients with Crohn's
disease have been treated with biologicals since 1995\textsuperscript{20} and therefore conclusions
drawn from this patient population are more advanced and reliable than from the HS
population. In summary, for patients with Crohn's disease infliximab has proven to be an
effective treatment when administered i.v. 5 mg/kg at weeks 0, 2, and 6 and subsequently
every 2 months. Subsequently etanercept s.c. 25 mg twice weekly was investigated and
turned out to be ineffective for patients with Crohn's disease. Then adalimumab was
investigated, and it appeared that in Crohn's disease, the optimal dosage was 160 mg
at week 0, followed by 80 mg at week 1 and subsequently 40 mg at alternate weeks.\textsuperscript{21}

It seems that TNF-\(\alpha\) inhibitors have a similar efficacy in both patients with Crohn's
disease and in patients with HS. Assuming that this observation is correct, for infliximab
the schedule should be identical to Crohn's disease, which means that after the initial
high loading dose, the patients should receive a maintenance therapy every 2 months
for as long as necessary. In our study, adalimumab turned out to be less effective
in doses of 40 mg every other week. A higher dose starting at 160 mg in week 1,
followed by 80 mg at week 2, followed by 40 mg every week instead of every other
week, may result in a better disease response.

The costs of long-term treatment with TNF-\(\alpha\) inhibitors are high. Since HS is not a
registered indication for biological treatments, many health insurances are not willing
to reimburse the costs. In the Netherlands, some health insurances take responsibility
and reimburse the off-label use of TNF-\(\alpha\) inhibitors for the most severe cases. In
contrast to other indications such as psoriasis, in which case long-term or even life-long
treatment is necessary, the use of TNF-\(\alpha\) inhibitors in HS may be limited to a shorter
period if treatment is followed by, or combined with, surgical interventions.\textsuperscript{22} Using this
combined approach, a percentage of the severe HS patients can be cured. With this
perspective, hopefully there will be more options in the future to treat patients with
severe HS with biologicals. These patients would benefit immensely from effective
treatment, as HS is a devastating disease. Its impact on quality of life is even higher
than for patients with psoriasis who receive TNF-\(\alpha\) inhibitors.\textsuperscript{2}
REFERENCES


CHAPTER 6

The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review

D.C. van Rappard, J. Limpens, J.R. Mekkes

ABSTRACT
To provide an overview of the current evidence regarding off-label treatment of hidradenitis suppurativa (HS) with TNF-α inhibitors, a systematic search was performed in MEDLINE, EMBASE and CENTRAL. Any type of original article concerning HS patients treated with infliximab, etanercept and/or adalimumab was included. No language restriction was applied. After full-text screening 65 studies involving 459 patients met the inclusion criteria and were subjected to data extraction. Four randomized controlled trials (RCTs) were available, and the remainders were case series or reports. Only RCTs were subjected to methodological quality assessment. Based on efficacy data extracted from the case reports, a moderate to good response was seen in 82% of the patients treated with infliximab, 76% of the patients treated with adalimumab, and 68% of the patients treated with etanercept. Due to the moderate level of evidence only a weak recommendation can be provided. If conventional treatment options fail, the use of TNF-α inhibitors can be a useful supplement for the treatment of recurrent severe HS. Infliximab should be preferred based on the most encouraging results regarding efficacy and expenses. Also adalimumab seems promising when administered in higher doses. The use of etanercept should be discouraged.
INTRODUCTION

Hidradenitis suppurativa (HS), also named acne inversa, is a chronic recurrent skin disease, characterized by deep-seated nodules, usually progressing to painful abscesses, sinus tracts and hypertrophic fibrous scars. The disease predominantly affects the inverse areas of the body, such as the axillary, inguinal and anogenital regions.¹

The severity of HS can be divided in three categories, ranging from mild, to moderate and severe, as suggested by Hurley.² In its severe form, HS is associated with a significant impairment of quality of life.³ The estimated prevalence is 1–4% with a female predominance. It is generally believed that the pathogenesis is initiated by follicular plugging followed by occlusion and dilatation of the pilosebaceous unit, bacterial super infection and gland rupture. The exact etiology is still unknown.⁴

HS together with acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus, make up the so-called follicular occlusion tetrad. Furthermore, HS has been associated with several other diseases including arthritis, pyoderma gangrenosum and Crohn’s disease.⁵

Many conservative therapies, such as topical antibacterial or antiseptic lotions, systemic antibiotics, corticosteroids, retinoids and hormonal therapy, seem to have a supportive character, achieving only temporary improvement. Many authors recommend surgical intervention to cure the condition.⁶

Over the last decade, promising results of TNF-α inhibitors (or so-called ‘biologicals’) have been reported. The first beneficial effect was reported in 2001, describing improvement of HS lesions after three infliximab infusions in a patient with Crohn’s disease and coexisting HS.⁷ Subsequently, the use of etanercept and the use of adalimumab were investigated.

In 2009, Haslund et al.⁸ performed a systematic search to evaluate the three biologics. A total of 34 publications were analyzed and promising results were reported for each. At that time, only case reports or series were available. Rationally, the need for randomized controlled trials (RCTs) was emphasized by the authors. In recent years, several RCTs did appear, making a systematic revision of literature be worthy again. This systematic review provides more extensive and stronger evidence to answer the question: What is the most effective TNF-α inhibitor for the treatment of patients with recalcitrant HS?

METHODS

Search strategy

A medical librarian (J.L.) with experience in conducting searches for systematic reviews, undertook a systematic search of the electronic databases OVID MEDLINE (1948–14 July 2011), OVID EMBASE (1980–14 July 2011) and CENTRAL (up to 11 March 2011) to identify studies on biological treatment of HS. Both free-text words and index terms specific to each database (i.e., MeSH in MEDLINE) for HS and for biological treatment with infliximab, adalimumab and etanercept were combined using the Boolean operators “AND” and “OR” (Table 1). Additionally, PubMed was searched for RTCs ahead of
print, not yet included in OVID MEDLINE. No methodological search filters or limits were applied. Reference Manager® software (version 12.0) was used to de-duplicate all identified references. Finally, reference lists of included articles were reviewed for additional relevant studies, not found in the above-mentioned electronic databases.

**Study selection**

All stages of the study selection, to identify conceivably relevant studies, were performed independently by two reviewers. Disagreements were resolved by consensus. Identified records from the search were screened on title and abstract to identify all articles concerning anti-TNF-α treatment and HS. To determine eligibility of the selected studies, full text was assessed according to the predefined inclusion and exclusion criteria. Articles were excluded if there was lack of relevance (i.e., no treatment of individual patient or patient group described) or if no outcome data on efficacy were provided. Also reviews, meta-analyses and double publications were excluded. No language restriction was applied. RCTs, cohorts, case series, case reports and abstracts from poster presentations concerning HS treated with infliximab, etanercept and/or adalimumab were included for data extraction. Additionally, we included two more data sets regarding our own experience with biological treatment for HS.

**Data extraction**

One of the review authors (D.R.) extracted data from the included studies. Another author (J.M.) checked all extracted data. Disagreements between reviewers were solved by discussion. General data concerning author, publication date, study design, number of patients, gender, associated diseases and efficacy of treatment, were extracted and summarized. Additionally, information on treatment schedule and dosage, co-medication, interruption of treatment and safety were collected. Information extracted from RCTs was more comprehensive, and duration of treatment, follow-up period, dosage and outcome were specified for each treatment arm. If a study provided sufficient information on efficacy of more than one TNF-α inhibitor, for example, due to patients switching therapy, data were separately included for each TNF-α inhibitor described.

**Methodologic quality**

RCTs were critically appraised using the Cochrane collaboration’s tool for assessing risk of bias.9 The following items were assessed: sequence generation, concealment of allocation, blinding of participants, researchers and outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity. When items were adequately reported, judgment with “yes” in case of low risk of bias, or “no” in case of high risk of bias, were adjusted. Insufficient information resulted in judgment with “unclear”. Case reports were not assessed for methodological quality.
### Table 1. Search strategy MEDLINE

| 1. | exp Hidradenitis/ |
| 2. | (h?draden* adj2 suppur*).tw. |
| 3. | (h?dradenitis or hidro?adenit*).tw. |
| 4. | (acne adj1 invers*).tw. |
| 5. | verneuil’s.tw. |
| 6. | (ectopic* adj2 acne*).tw. |
| 7. | or/1-6 |
| 8. | (biologicals or biologics or ((biological or biologic or targeted) adj (treatment or therap* or medicine* or drug* or agent* or product*) or ag).tw. |
| 9. | Tumor Necrosis Factor-alpha/ai, ag |
| 10. | Receptors, Tumor Necrosis Factor/tu |
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| 16. | (fusion adj2 protein*).tw. |
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| 18. | alefacept.tw,ot,rn. |
| 19. | Antibodies, Monoclonal/tu, ae, ad |
| 20. | Immunoglobulin G/tu, ae, ad |
| 21. | (chim?eric adj (monocl* or antibod* or Abs or Moab*)).tw. |
| 22. | infliximab.tw,ot,rn. or (avakine or remicade).tw,ot. |
| 23. | adalimumab.tw,ot,rn. or (humira or D2E7 or trudexa).tw,ot. |
| 24. | or/8-23 |
| 25. | 7 and 24 |

/?: follows a MeSH-term.
exp (preceding a MeSH-term): explosion of a MeSH term (lower terms in hierarchy are also searched).
Subheadings (following a MeSH/): tu = therapeutic use, ae = adverse effect, ad= administration and dosage, ai = antagonists and inhibitors, ag = agonists.
.tw.: textword (word in title and/or abstract).
.ot.: word in the original title.
.rn.: CAS registry numbers.
*: truncation (all possible suffix variations of the root word).
?: optional wild card character, substituting for one or no characters.
Adj: a positional operator finding two terms next to each other in the specified order.
Adj(n): a positional operator that retrieves records containing the searched terms (in any order) within a specified number (n) of words of each other.
or/1-6: 1 or 2 or 3 or 4 or 5 or 6.
**Strength of evidence and recommendation**

Included studies were assessed regarding level of evidence according to six categories (IA, IB, IIA, IIB, III and IV). Based on the level of evidence, together with effects, burden, adverse events and costs, recommendations for treatment choice were proposed.10

**RESULTS**

*Literature search and selection*

The initial database research resulted in a total of 286 hits. The selection process is summarized in Fig. 1. After removing 90 duplicate entries and adding 5 records identified through other sources, 201 articles were eligible for screening. After full text screening, 65 studies met the inclusion criteria and were analyzed. The main reasons for exclusion were review studies and lack of relevance. Only four RCTs were available, and the remainders were case series or reports. No cohort studies were identified. Six studies described treatment efficacy for two separate TNF-α inhibitors and two studies provided information of all three biologics. This resulted in 44 studies concerning infliximab, 13 studies concerning etanercept and 18 studies concerning adalimumab.

![Flowchart providing an overview of the selection process.](image-url)
Data extraction included case reports

Infliximab

Infliximab (REMICADE®) has officially been registered for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque-type psoriasis, Crohn’s disease and ulcerative colitis. HS is still an off-label indication for infliximab and other biologics (Table 2).

So far, 16 case series and 26 case reports revealed data on efficacy of infliximab treatment for HS. Together with 16 of our patients, not earlier described, 43 studies describing 114 patients were available for analysis.

A standard dosage of 5 mg/kg was administered in nearly all patients. In three studies the dosage was increased to 7.5 or 10 mg/kg if necessary. In seven studies data on dosage were missing. Thirty-five patients (31%) only received an induction regime limited to three infusions, including six patients who improved after receiving only one or two infusions. In 70 patients (61%), the induction regime was followed by maintenance treatment, and for 9 patients (8%) no information regarding treatment duration was available. Regarding maintenance treatment, in 16 studies patients received infliximab according to the treatment schedule as used for Crohn’s disease, starting at weeks 0, 2 and 6, and subsequently every 8 weeks. For other studies the treatment intervals varied or data were absent.

A moderate or good response to infliximab treatment was observed in 94 patients (82%), and in 32 patients (28%) the response sustained for more than 3 months after treatment discontinuation. Efficacy of infliximab was poor or absent in 20 patients (18%). In 15 patients response decreased during continuous treatment. Withdrawal of infliximab treatment and re-introduction because of recurrence occurred in six patients, accompanied by infusion reactions in two of them. Nineteen studies reported occurrence of adverse events. Consequently, 23 patients (20%) were forced to discontinue infliximab treatment. One patient died from a pneumococcal sepsis, which was regarded as an opportunistic infection after receiving infliximab infusions for 2 years.

Etanercept

Etanercept (ENBREL®) is currently approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

So far, 12 studies including 5 case series and 7 case reports, revealed data on efficacy of etanercept. Data on a total of 44 patients were available for analysis.

Regarding dosage schedule, all patients were treated with subcutaneous injections of 25 or 50 mg once or twice a week. In three studies, patients started with a dose of 25 mg weekly, but increased to 50 mg weekly due to inefficacy. On the contrary, in two studies treatment was initiated at 50 mg once or twice a week and later tapered off to 25 mg.
Table 2. Results from case reports

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<td>5  5</td>
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<td>1  1</td>
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<tr>
<td>Year</td>
<td>Design</td>
<td>Associated diseases</td>
<td>Number (gender)</td>
<td>Effect during treatment</td>
<td>Prolonged effect</td>
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<tr>
<td>Delage et al.⁴⁹</td>
<td>2011</td>
<td>CS retro</td>
<td>7(4F,3M)</td>
<td>1</td>
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<tr>
<td>van Rappard et al.⁵⁰⁺</td>
<td>2011</td>
<td>CS retro</td>
<td>3(1F,2M)</td>
<td>3</td>
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<tr>
<td>Husein-ElAhmed et al.⁵¹</td>
<td>2011</td>
<td>CR, CD</td>
<td>1(M)</td>
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<tr>
<td>Unpublished data</td>
<td>2011</td>
<td>CS retro, CR, DC, PG, SP</td>
<td>16(6F,10M)</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

**Etanercept**

Jurgensmeyer and Fleischer⁵² | 2004   | CR                  | 1(F)           |                        |                 |

Cusack and Buckley²³ | 2006   | CS pros, CD         | 6(F)           | 1                      | 5               |

Henderson⁵⁴ | 2006   | CR                  | 1(F)           |                        |                 |

Giamarellos-Bourboulis et al.⁵⁵† | 2008   | CS pros             | 10(7F,3M)      | 3                      | 7               | 10              |

Zangrilli et al.⁵⁶ | 2008   | CR, AC              | 1(M)           |                        |                 |

Lee et al.⁵⁷ | 2009   | CS pros             | 15(13F,2M)     | 11                     | 4               |

Sotiriou et al.⁵⁸ | 2009   | CS pros             | 4(3F,1M)       | 1                      | 3               | 1               |

Poulin⁵⁷ | 2009   | CR, AC              | 1(F)           |                        |                 |

Blanco et al.⁵⁹ | 2009   | CR                  | 1(F)           |                        |                 |

Moran et al.⁶⁰ | 2009   | CS retro, AR         | 2(F)           |                        |                 |

Hsiao et al.⁴² | 2010   | CR                  | 1(F)           |                        |                 |

Fernandez et al.⁴⁷ | 2010   | CR                  | 1(F)           |                        |                 |

**Adalimumab**

Ravat et al.¹⁸ | 2005   | CR                  | 1(M)           |                        |                 |

Scheinfeld⁶¹ | 2006   | CR, AC, AR, PG       | 1(M)           |                        |                 |

Moul and Korman⁶² | 2006   | CR, CD              | 1(M)           |                        |                 |

Sotiriou et al.⁶³ | 2009   | CS pros             | 3(F)           |                        |                 |

Yamauchi and Mau⁶⁹ | 2009   | CR, AR, PS          | 3(F)           |                        |                 |

Harde and Mrowietz⁶⁴ | 2009   | CR                  | 1(M)           |                        |                 |

Blanco et al.⁶⁵ | 2009   | CS pros             | 6(4F,2M)       |                        |                 |

Moran et al.⁶⁰ | 2009   | CS retro, AR         | 3(F)           | 1                      | 1               | 1               |

Hsiao et al.⁴² | 2010   | CR, AC              | 1(M)           |                        |                 |

Koilakou et al.⁶⁵ | 2010   | CR, AC, CD, SP       | 1(M)           |                        |                 |

Amano et al.⁶⁶ | 2010   | CS pros             | 10(7F,3M)      | 10                     |                 |

Alzaga Fernandez et al.⁶⁷ | 2010   | CR                  | 1(F)           |                        |                 |

Arenbergerova et al.⁶⁸ | 2010   | CS pros             | 8(5F,3M)       |                        |                 |

Fernandez et al.⁴⁷ | 2010   | CS pros, AR, PS       | 18(9F,9M)     | 1                      | 4               | 13              |

van Rappard et al.⁵⁰⁺ | 2011   | CR                  | 1(M)           |                        |                 |

van Rappard et al.⁵⁰⁺‡ | 2011   | CS pros             | 9(1F,8M)       | 2                      | 3               | 4               |

* Two of the five cases treated with infliximab were described in earlier studies by Mekkes et al.
† Additional follow up data were published by Pelekanou et al. in 2010.
‡ Study was yet accepted but not included in the search.
Italic: study describes treatment with more than one TNF-α inhibitor.
AC = acne conglobata; AR = arthritis; AS = ankylosing spondylitis; CD = Crohn’s disease; CU = colitis ulcerosa; DC = dissecting cellulitis of the scalp; PC = pachyonychia congenita; PG = pyoderma gangrenosum; PS = psoriasis; SP = sinus pilonidal.
A moderate or good response to etanercept treatment was observed in 30 patients (68%), and in 11 patients (25%) the response sustained for more than 3 months after treatment discontinuation. In 14 patients (32%), the response was poor or absent. In two patients, the response decreased during continuous treatment. Suspension of etanercept treatment and re-introduction because of recurrence of HS lesions occurred in 13 patients.

Adverse events were reported in five studies. Overall, four patients (9%) had to discontinue etanercept treatment due to adverse events.

**Adalimumab**

Adalimumab (HUMIRA®) is currently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, plaque psoriasis and juvenile idiopathic arthritis.

Until now, 16 studies including 8 case series and 8 case reports, revealed data concerning the efficacy of adalimumab treatment for HS. Altogether, 68 patients were available for data extraction.

The majority (46 patients in 10 studies) was treated with 40 mg subcutaneously every other week. In one study, adalimumab was administered every week. In five studies, the dosage was increased from 40 mg every other week to 40 mg weekly if necessary to maintain clinical improvement. Three studies (19 patients) started with a higher initial dose of 80 or 160 mg. In the three remaining studies no data on doses or intervals were available.

A moderate or good response was observed in 52 patients (76%), and in 8 patients (12%) the response sustained for more than 3 months after treatment discontinuation. The response was poor or absent in 16 patients (24%). Withdrawal and reintroduction of adalimumab occurred in two patients, for one due to insurance problems and for the other due to an adverse event (facial cellulitis). Additionally, one other patient had to discontinue treatment due to an adverse event, without re-introduction later on. Overall, adverse events were reported in five studies.

**Data extraction included randomized controlled trials**

**Infliximab**

The first RCT of anti-TNF-α treatment for patients with HS appeared in 2010. Grant et al. assessed the efficacy and safety of infliximab for the treatment of moderate to severe HS in 38 patients (26 female, 12 male). This 52 weeks during trial consisted of a double-blind placebo-controlled phase, an open-label crossover phase where patients taking placebo were given the opportunity to receive infliximab, and an observational phase. During the initial 8 weeks, patients received either infliximab i.v. (5 mg/kg at weeks 0, 2 and 6, and subsequently every 8 weeks) or placebo and afterward the primary efficacy point was assessed. More patients in the infliximab
group showed a 50% or greater decrease from baseline in the HS severity score ($p = 0.092$). Also secondary outcomes, including Dermatology Life Quality Index (DLQI), Visual Analog Scale (VAS) and Physician Global Assessment (PGA), showed a significantly greater improvement after 8 weeks. The mean DLQI score decreased 10 points in the infliximab group versus 1.6 points in the placebo group ($p = 0.003$). Of the six DLQI subscores, five improved significantly: ‘symptoms and feelings’, ‘daily activities’, ‘leisure’, ‘personal relationships’ and ‘work and school’ (Tables 3 and 4).

The mean decrease in VAS pain score was 39.8 for the infliximab group versus a decrease of 0.6 for the patients receiving placebo ($p < 0.001$). The PGA scores differed 2.9 points between both groups, again in favor of infliximab ($p < 0.001$). Only five patients continued the trial through week 52, and two of them had a protracted response. Adverse events occurred in 15 patients of the original infliximab group. They were mostly mild and included influenza-like illness, myalgia, dizziness and headache. Two serious adverse events (a pregnancy and hypertension) were reported. Adverse events in the placebo group were higher, including one serious adverse event (infusion reaction). This study confirmed the efficacy of infliximab for HS treatment.

**Etanercept**

In accordance with the sequence in which case reports of TNF-α inhibitors for HS appeared, the second RCT on the subject investigated the use of etanercept. Adams et al.\(^7\) described 20 patients (13 female, 7 male) randomly assigned to either etanercept 50 mg subcutaneously or placebo. After 12 weeks all patients received open-label etanercept for 12 more weeks. The primary efficacy point was the PGA of clear or mild, assessed at week 12. No statistically significant difference in PGA between treatment and placebo was observed ($p > 0.99$). Also, none of the secondary end points including Patient Global Assessment ($p = 0.41$) and DLQI ($p = 0.12$), were significantly improved. No serious adverse events occurred, only some mild injection site reactions were reported. As a consequence of these negative results, the off-label use of etanercept in HS has been discouraged by the manufacturer.

**Adalimumab**

Two RCTs were available for adalimumab. Initially, Miller et al.\(^2\) described 21 patients (17 female, 4 male) with moderate to severe HS, randomly assigned to adalimumab (80 mg at week 0 followed by 40 mg every other week) or placebo. The primary efficacy end points included change in HS scoring systems as proposed by Sartorius and Hurley after 12 weeks of treatment. A significant reduction was gained for solely the Sartorius score after 6 weeks, but not after 12 weeks of active treatment (-11.3 vs 5.8, $p = 0.07$). Also, secondary outcomes including VAS pain and DLQI scores lacked significance after 12 weeks, indicating only short-term efficacy. The mean VAS change from baseline for patients treated with adalimumab was -13.4 versus +3.17 for placebo ($p = 0.4$). The mean DLQI...
<table>
<thead>
<tr>
<th>Author/Years</th>
<th>Design</th>
<th>Treatment arms</th>
<th>Treatment duration RCT wk (doses)</th>
<th>Treatment duration open label wk (doses)</th>
<th>Follow up no treatment wk</th>
<th>Number of patients (gender)</th>
<th>Mean age</th>
<th>Primary efficacy point</th>
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<tbody>
<tr>
<td>Grant et al, 2010</td>
<td>RCT</td>
<td>IFX i.v.</td>
<td>8 (5 mg/kg)*</td>
<td>14 (5 mg/kg)</td>
<td>30</td>
<td>15 (12F,3M)</td>
<td>34.0</td>
<td>HSSI (wk 8)</td>
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<td>Placebo (IFX)</td>
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<td>22</td>
<td>23 (14F,9M)</td>
<td>33.2</td>
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<tr>
<td>Adams et al, 2010</td>
<td>RCT</td>
<td>ETA s.c.</td>
<td>12 (50 mg 2x/wk)</td>
<td>12 (50 mg 2x/wk)</td>
<td>0</td>
<td>10 (6F,4M)</td>
<td>40.0</td>
<td>PGA (wk 12)†</td>
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<td>Placebo (ETA)</td>
<td>12 (50 mg 2x/wk)</td>
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<td>10 (7F,3M)</td>
<td>36.7</td>
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<tr>
<td>Miller et al, 2011</td>
<td>RCT</td>
<td>ADA s.c.</td>
<td>12 (80 mg, 40 mg eow)</td>
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<td>15 (12F,3M)</td>
<td>38.7</td>
<td>HSSS (wk 12)</td>
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<tr>
<td>Kimball et al, 2011</td>
<td>RCT</td>
<td>ADA s.c. ew</td>
<td>16 (160 mg, 80 mg, 40 mg ew)</td>
<td>36 (40 mg eow)</td>
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<td>51 (36F,15M)</td>
<td>35.1</td>
<td>PGA (wk 16)‡</td>
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<tr>
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<td>51 (36F,15M)</td>
<td>37.8</td>
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</table>

*Start at weeks 0, 2, 6 and subsequently every 8 weeks.
†Achievement of PGA clear or mild.
‡Achievement of PGA clear, minimal or mild, with a minimum of 2 grades improvement from baseline.
ADA = adalimumab; eow = every other week; ETA = etanercept; ew = weekly; HSSI = Hydradenitis Suppurativa Severity Index; HSSS = Hydradenitis Suppurativa Scoring Systems (Hurley and Sartorius); IFX = infliximab; PGA = Physician Global Assessment; RCT = randomized controlled trial; wk = week.
changed -3.67 versus +1 in the placebo group (p = 0.06). Adalimumab was well tolerated, but more adverse events were observed in the adalimumab group compared with placebo.

Subsequently, Kimball et al. investigated adalimumab in higher doses, in a three arm RCT of 154 participants (110 female, 44 male). Fifty-one patients received adalimumab every week (after 160 mg at week 0 and 80 mg at week 2), 52 patients received adalimumab every other week (after 80 mg at week 0) and 51 patients received placebo. The primary efficacy end point was the proportion of patients who achieved a PGA score of clear, minimal or mild, with at least two-grade improvement relative to baseline. At week 16, the proportion of patients achieving success was 17.6%, 9.6%, 3.9% for every week, every other week and placebo, respectively with only a significant difference between the every week and placebo group (p = 0.025). In the same order, the DLQI scores improved with 6.0, 2.8 and 1.9 (p < 0.001 every week vs placebo). Furthermore, the proportion of patients achieving at least 30% reduction in VAS pain score was 47.9%, 36.2%, 27.1% (p = 0.036 every week vs placebo) and again no significant difference was found for the every other week group compared with placebo. Serious adverse events rates were low and similar across treatment groups. In conclusion, adalimumab results in a better disease response when administered in higher dosage.

**Methodologic quality and strength of evidence**

The risk of bias varied between the RCTs as shown in Table 5. Adequate randomization was described in three studies and was unclear in one study. Blinding of participants and assessors was judged as adequate for all studies. Information on blinding researchers was missing in one study. All studies were subjected to other sources of bias due to...
funding. However, Adams et al. explicitly reported that only the study medication was sponsored and that the sponsors had no role in the design and conduct of the study. Another source of bias was noticed in the study of Miller et al. They included fewer patients than was calculated in advance to achieve sufficient power. This may also explain the observed baseline imbalance.

**CONCLUSION**

Based on efficacy data that were extracted from the case reports, a conclusion can be drawn. Infliximab appears to be the most effective biologic, achieving a moderate to good response in 82% of the patients, followed by adalimumab which turned out to be effective in 76% of the patients. The lowest percentage of responders (68%) was seen after etanercept treatment. Subsequently, the RCTs support this conclusion and confirm the efficacy of infliximab, partly confirm the efficacy of adalimumab (effective when administered in higher dosage) and discourage the use of etanercept.

**DISCUSSION**

This systematic review provides an overview of the current evidence regarding off-label treatment of HS with TNF-α inhibitors. Especially infliximab and adalimumab seem to be a promising supplement for the treatment of recalcitrant HS, however, the role of etanercept seems to be doubtful.

The same pattern can be recognized when comparing the efficacy of TNF-α inhibitors in patients with HS to their efficacy in patients with Crohn’s disease. For patients with Crohn’s disease infliximab has proven to be an effective treatment when administered i.v. 5 mg/kg at weeks 0, 2 and 6, and subsequently every 8 weeks.
Subsequently, etanercept s.c. 25 mg twice weekly was investigated and turned out to be ineffective. Then adalimumab was investigated and turned out to be effective as well, with the optimal dosage of 160 mg at week 0, 80 mg at week 2 and subsequently 40 mg at alternate weeks. Eventually, infliximab and adalimumab have been approved by the Food and Drug Administration for the treatment of Crohn’s disease.

In case of HS, adalimumab turned out to be less effective in doses of 40 mg every other week. A higher dose, starting at 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg weekly instead of every other week, resulted in a better disease response. Consequently, in five studies it was necessary to increase the dosage from 40 mg every other week to 40 mg weekly to maintain clinical improvement. Unfortunately, this higher dosage requirement is accompanied by increasing costs, making adalimumab treatment almost twice as expensive as standard infliximab treatment. The expenses on etanercept treatment (50 mg weekly) lay between those two extremes. Since HS is not a registered indication for biological treatments, many health insurances are not willing to reimburse the costs, and defrayment can be a problem.

Despite the higher costs, an advantage of adalimumab (and etanercept) is that after instructions, it can be self-administered as subcutaneous injections, unlike infliximab which always has to be administered in a hospital setting, intravenously. Also, data regarding safety extracted from case reports were in favor of adalimumab (and etanercept). Obligatory discontinuation of treatment due to adverse events was most frequently observed in patients treated with infliximab (20%), followed by adalimumab (9%) and etanercept (3%). However, this pattern was not observed in the RCTs.

Some considerations should be taken into account when interpreting the results of this review. The majority of included studies were case reports addressing new, promising treatment options for a recalcitrant dermatosis, and therefore positive publication bias may account for some of the effect we observed. Also, in several studies concomitant medication was allowed, which may have contributed to a positive result. Moreover, information on co-medication was frequently missing.

The sometimes scarce information on treatment schedule, differences in dosage and administration route, made comparison of the three biologics hard. Also evaluation methods used in the studies were neither uniform, nor extensive. Astonishingly, the DLQI was used consistently in all RCTs and also frequently in the remaining case reports: 5/43 (12%) studies on infliximab, 5/12 (42%) studies on etanercept and 6/16 (38%) studies on adalimumab. One study used the Skindex-29 to assess quality of life. As HS can be a devastating disease, assessment of quality of life is of great importance. Its impact on quality of life is said to be even higher than for patients with psoriasis who receive TNF-α inhibitors. Smoking habits calculated from the scarce available case reports that assessed them, revealed high percentages: 83%, 100%, 95% for infliximab, etanercept and adalimumab, respectively. This is not surprising, as HS is strongly correlated with cigarette smoking. Unfortunately, from two RCTs baseline characteristics of smoking habits were not available.
The attempts to find a cure for HS continue. More recently developed TNF-α inhibitors, including certolizumab pegol and golimumab have not yet been investigated for their treatment of HS, as they are not yet approved for other dermatological purposes. Two other kinds of monoclonal antibodies have been investigated for their efficacy in HS, ustekinumab and efalizumab. Investigation of the former showed promising results and the latter did not.76,77

RECOMMENDATION

Based on the scarce amount of RCTs supported by additional case reports, the quality of evidence is for all three biologics limited (IB). Therefore, only a weak recommendation for the use of infliximab, etanercept and adalimumab for the treatment moderate to severe HS can be provided (Table 6).

Larger and better conducted RCTs regarding TNF-α treatment with a longer follow-up duration are warranted to make systematic reviews on this matter more accurate.

Table 6. Recommendation

<table>
<thead>
<tr>
<th>TNF-α inhibitor</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>IB</td>
<td>If conventional treatment options fail or are contraindicated, the use of infliximab (5mg/kg at week 0, 2, 6 and every 8 weeks) should be preferred based on the most encouraging results regarding efficacy and expenses. Attention should be paid to safety aspects when prescribing infliximab.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>IB</td>
<td>If conventional treatment options fail or are contraindicated, adalimumab may be a useful alternative when administered in higher doses starting with 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>IB</td>
<td>A weak recommendation against the use of etanercept for the treatment of HS can be given. It is unclear whether the effort and risks outweigh the benefits.</td>
</tr>
</tbody>
</table>

*Level of evidence categories: IA meta-analysis of randomized controlled trials; IB at least one randomized controlled trial without randomization; IIB at least one other type of experimental study; III non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; IV expert committee reports or opinions or clinical experience of respected authorities, or both.

HS = hidradenitis suppurativa; RCT = randomized controlled trial.

REFERENCES

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New-onset polyarthritis during successful treatment of hidradenitis suppurativa with infliximab

D.C. van Rappard, J.E. Mooij, D.L.P. Baeten, J.R. Mekkes

British Journal of Dermatology 2011; 165: 194-8
ABSTRACT

Background: Hidradenitis suppurativa (HS) can be associated with several forms of arthritis, usually considered as reactive arthritis. A new observation is that some patients with HS develop arthritis after treatment with infliximab (antitumour necrosis factor-α).

Objectives: A retrospective study was performed to establish the frequency and clinical presentation of new-onset arthritis during infliximab treatment.

Methods: Between 2005 and 2009, 27 individuals with severe HS were treated with infliximab and followed up closely. Laboratory parameters and side-effects were recorded. The frequency of arthritis was compared with control groups consisting of 227 patients with not treated with any biological, 22 patients with HS treated with adalimumab and 28 patients with psoriasis treated with infliximab, in the same period at the same clinic.

Results: Five of the 27 patients with HS (18%) treated with infliximab developed an acute and painful polyarthritis during treatment. The arthritis occurred on average after 12 months of treatment, was not clearly associated with anti-infliximab antibodies and resolved on average after 4 months. Interestingly, none of the patients had suffered from arthritis before despite the long duration of HS and all showed a good skin response to infliximab. Moreover, arthritis was not observed in any of the control groups. Compared with the adalimumab group and the psoriasis group, odds ratios of 7.241 [95% confidence interval (CI) 1.15–45.6] and 9.025 (95% CI 1.45–55.82) were calculated.

Conclusions: The five cases described in this article suggest that infliximab treatment in HS can induce a transient but severe polyarthritis. The underlying mechanisms remain to be investigated further.
INTRODUCTION

Hidradenitis suppurativa (HS), also called acne inversa, is a chronic skin disease characterized by purulent inflammation of occluded hair follicles and sebaceous glands, leading to abscesses, scars and sinus tract formation. Typically affected areas are the axilla and groin. HS together with acne conglobata and dissecting cellulitis of the scalp, has been classified as the ‘follicular occlusion triad’.1,2 Other diseases that are associated with HS are Crohn disease, pyoderma gangrenosum and psoriasis.3,4

In patients with combined HS and Crohn disease, it was observed that treatment of the inflammatory bowel disease with infliximab [antitumour necrosis factor (TNF)-α] resulted in dramatic improvement of their HS. The first case report appeared in 2001.5 In 2003, the first patients with isolated HS without Crohn disease were treated successfully with infliximab.6 Since then, the number of patients with HS treated with infliximab and other TNF-α inhibitors, such as etanercept and adalimumab, has gradually increased.7,8 Based on the cumulative case reports, in 2008, the Dutch healthcare organization approved the reimbursement of infliximab for severe therapy-resistant cases.

Approximately 100 patients with HS have been treated with infliximab in the Netherlands, including 27 patients in our hospital. These patients were closely monitored for efficacy and potential side-effects. Here, we describe the unexpectedly high frequency and the phenotype of new-onset polyarthritis in patients with HS treated with infliximab.

METHODS

Between 2005 and 2009, 27 patients with severe therapy-resistant HS were treated with infliximab infusions (5 mg kg\(^{-1}\) at weeks 0, 2 and 6 and subsequently every 2 months). Severe therapy-resistant HS was defined as Hurley stage III, not responding to systemic antibiotics including the combination of clindamycin and rifampicin. Patients were strictly followed up with a steady interval of 2 months. Side-effects were recorded. Special attention was paid to the occurrence of rheumatological symptoms: the time of onset after the first infliximab infusion, the joints involved and the duration of symptoms were all recorded, and the patients were referred to the rheumatologist for further evaluation. At the start of the first signs of arthritis, laboratory parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leucocyte count, rheumatoid factor and antibodies to infliximab were determined. As control groups, we used a cohort of 227 patients with HS not treated with any biological, 22 patients with HS treated with adalimumab for 1 year, and 28 patients with psoriasis treated with infliximab according to the same schedule used for the 27 patients with HS. The 22 patients on adalimumab and the 28 patients with psoriasis were also treated under study conditions, during the same period and were monitored closely, and were followed up for at least 1 year.
RESULTS

In total, 27 patients with severe therapy-resistant HS were treated with infliximab infusions (21.4 patient-years). Five of these patients (18%) developed an acute and painful polyarticular arthritis (mainly knees, elbows, wrists and fingers) during treatment, which made it necessary to discontinue treatment (Table 1). None of them had suffered from arthritis before, despite the long duration of severe HS (average duration 20 years). The mean time between the start of treatment and the first symptoms of arthritis was 12 months (range 0.3–23), and after eight infusions (range 1–15), and the mean duration of arthritis symptoms was 4 months. Their cases are described below. In the same period, 22 patients with HS were treated with adalimumab and 28 patients with psoriasis were treated with infliximab. In these groups no development of arthritis was observed. Arthritis was significantly more frequently observed in the 27 patients with

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Patient 1</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Duration of hidradenitis (years)</td>
</tr>
<tr>
<td>Previous arthritis</td>
</tr>
<tr>
<td>Number of infusions</td>
</tr>
<tr>
<td>Treatment result on HS</td>
</tr>
<tr>
<td>Duration of infliximab treatment at onset of arthritis (months)</td>
</tr>
<tr>
<td>ESR before treatment (mm h&lt;sup&gt;−1&lt;/sup&gt;)</td>
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<tr>
<td>ESR at start of arthritis (mm h&lt;sup&gt;−1&lt;/sup&gt;)</td>
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<tr>
<td>Leucocytes at start arthritis (10&lt;sup&gt;9&lt;/sup&gt; L&lt;sup&gt;−1&lt;/sup&gt;)</td>
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<tr>
<td>Polyarticular arthritis</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
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<tr>
<td>Infliximab antibodies (AU mL&lt;sup&gt;−1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Treatment of arthritis</td>
</tr>
<tr>
<td>Paracetamol</td>
</tr>
<tr>
<td>NSAID</td>
</tr>
<tr>
<td>Tramadol</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Methotrexate</td>
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<tr>
<td>Duration of arthritis (months)</td>
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</table>

HS, hidradenitis suppurativa; ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug. <sup>a</sup>This patient had been treated with three infliximab infusions 3 years earlier.
HS treated with infliximab compared with the adalimumab control group [odds ratio (OR) 7.241, 95% confidence interval (CI) 1.15–45.6] and the psoriasis control group (OR 9.025, 95% CI 1.45–55.82). Also, in the same period, 227 patients with HS were not treated with any biological, and no development of arthritis was observed in this group.

Case 1
Patient 1 is a 45-year-old woman who has had severe HS for 27 years. After the fifth infusion she developed myalgia and acute and severe polyarthritis of the elbows, knees, wrists and fingers. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone for 6 weeks was necessary. Infliximab treatment was discontinued. Her HS had responded very well to the infliximab infusions and fortunately did not recur (Fig. 1). The patient is still completely free of lesions after 5 years of follow-up.

Case 2
Patient 2 is a 44-year-old man who has had HS for 15 years. Because of severe HS, infliximab was initiated in 2006. After 23 months he developed arthritis of the knees, elbows and metacarpophalangeal joints. Treatment with NSAIDs, methotrexate and prednisone was necessary to control the arthritis. After discontinuation of infliximab, the arthritis diminished but new HS lesions appeared. Adalimumab was started, with good results. Prednisone was stopped and methotrexate was reduced to 7.5 mg weekly. Arthritis did not reappear during the adalimumab treatment.

Case 3
Patient 3 is a 42-year-old woman with a 30-year history of HS. After 9 months of treatment with infliximab she developed myalgia in the upper arms and upper legs and acute arthritis of the wrists and metacarpophalangeal joints. Infliximab was discontinued. The arthritis remained active for 3 months and was treated with paracetamol and NSAIDs. The HS lesions disappeared and did not recur (current follow-up duration 15 months).

Case 4
Patient 4 is a 59-year-old man with an 8-year history of HS and perianal fistulas. After 20 months of treatment with infliximab he developed arthritis in the knees, wrists and hands. The rheumatoid factor was positive (148 kU L\(^{-1}\)), antibodies against infliximab were present (310 AU mL\(^{-1}\)). The arthritis was treated with NSAIDs and diminished after 8 months. The HS was not sufficiently under control; new lesions appeared after discontinuation of infliximab.

Case 5
Patient 5 is a 54-year-old man with severe HS for 29 years who was treated with infliximab in 2004. He received three infusions, responded well to the treatment and no side-effects
were observed. In 2007, his HS started to recur and infliximab was given again. Ten days after the infusion, he developed arthritis in both knees, accompanied by myalgia. The knees were swollen, red and warm and he was unable to walk. High levels of antibodies against infliximab were present (3000 AU mL\(^{-1}\)), rheumatoid factor was negative. The arthritis was treated with an NSAID and resolved within 5 weeks. The HS is still active.

**DISCUSSION**

In this case series, we describe new-onset polyarthritis in five out of 27 patients with HS treated with infliximab. In one patient (case 5), the previous exposure to infliximab, the high-titre anti-infliximab antibodies, the timing of onset and the phenotype of the disease are compatible with serum sickness. In the other cases, the disease presented as an acute, painful polyarthritis occurring after several months of successful treatment of the skin disease with infliximab.

Because a large number of patients with inflammatory bowel disease, rheumatoid arthritis, spondyloarthritis or psoriasis have been treated with infliximab worldwide, there is sufficient knowledge about the short-term and long-term side-effects that may occur.\(^{10}\) Arthritis is not a common side-effect of treatment with infliximab. Temporary arthralgia combined with myalgia and fever is a possible side-effect (frequency 1 : 100 to 1 : 1000). This usually occurs 12 days after infusion, especially after the second

![Figure 1. Patient 1: improvement of hidradenitis suppurativa lesions in the left axilla after infliximab treatment (left image, before treatment; right image, still free of symptoms after 3 years).](image)
infusion, and is regarded as a serum sickness-type delayed allergic reaction.\textsuperscript{11} Two case reports describe reactive arthritis under treatment with infliximab, caused by bacterial sepsis (\textit{Moraxella catarrhalis} and \textit{Salmonella enteritidis}).\textsuperscript{12,13} The occurrence of an acute, severe polyarthritis during infliximab treatment has not been described in the registered indications. In the HS patient group described in this study, however, it is likely that the arthritis is directly related to infliximab treatment because none of the patients had had arthritis before initiation of treatment and all arthritis symptoms disappeared completely after discontinuation of treatment.

HS can be associated with rheumatological symptoms independently of infliximab treatment. The first association between HS, acne conglobata and arthritis in 10 patients was described in 1982.\textsuperscript{14} Since then, several cases of HS and co-occurrence of arthritis have been published.\textsuperscript{15–20} These include axial as well as peripheral arthritis, and occasionally enthesopathy.\textsuperscript{16,18} In case of axial involvement, there is a predilection for the sacroiliac joint.\textsuperscript{18} Peripheral arthritis mostly affects the knees, wrists, elbows and ankles, in both symmetrical and asymmetrical distribution.\textsuperscript{19} The exact frequency of arthritis in HS is unknown but probably low considering the small number of case reports. Accordingly, we did not observe any case of arthritis in 227 patients with HS treated with conventional therapies or in 22 patients with HS treated with adalimumab during the same period in our centre.

A limitation of our study is that it is retrospective, and that the TNF-\(\alpha\) treated patients were monitored more closely than the reference group of 227 patients with HS treated with conventional therapies. Nevertheless, the occurrence of acute and severe polyarthritis in five out of 27 cases treated with infliximab is remarkable, and it is unlikely that it can be explained by the rare spontaneous association of HS with rheumatological symptoms.

The pathogenesis of arthritis in HS remains unclear. Several suggestions for genetic, autoimmune and infectious mechanisms are proposed. In patients with HS linked to rheumatological abnormalities, rheumatoid factor and antinuclear antibodies are typically absent, and aspirate from the involved joints is often sterile. Furthermore the histocompatibility antigen HLA-B27 is mostly absent in contrast to other types of spondyloarthritis.\textsuperscript{17}

Nevertheless, arthritis in patients with HS is mostly described as reactive.\textsuperscript{14,20} Almost always the cutaneous manifestations of HS precede the onset of the arthritis. One of the hypotheses behind this reactive mechanism is that cutaneous infection may be a trigger for developing arthritis. Either the bacteria or, more likely, the immune response to the bacteria could be causing the articular manifestations. Circulating immune complexes and complement activation that have been observed in these patients may provoke rheumatological symptoms.

Several case reports suggest a relationship between the severity of the HS and the presence of rheumatological symptoms.\textsuperscript{15} Strikingly, however, the polyarthritis observed in the described cases occurred despite manifest improvement of the skin disease as evaluated by acne skin scores, Dermatology Life Quality Index and laboratory
parameters. The mean ESR at the moment of first onset of arthritis was 29 mm h\(^{-1}\), a 55% reduction compared with baseline values (Table 1). In none of the five patients reported above were there any signs of a flare in HS, an increased bacterial load or a bacterial infection. Importantly, there were no signs of septic arthritis which may have been caused by a combination of HS-related bacteraemia and immunosuppression by TNF blockade. In this context it is also important to note that we did not observe similar arthritic episodes in patients with HS treated with adalimumab.

Finally, it needs to be noted that paradoxical reactions to TNF blockade have been reported previously. Most typically, patients with arthritis may develop new-onset psoriasis-like lesions during treatment with TNF blockers despite a good articular response. Although the exact mechanism remains speculative, it is unlikely that a similar mechanism is operative in the cases described here as we observed exactly the opposite: new-onset joint disease despite skin improvement. Interestingly, induction of arthritis has also been described in patients with psoriasis treated with efalizumab. Taken together, these observations remain unexplained but indicate an uncoupling of inflammatory joint and skin disease in these conditions.

In conclusion, the high incidence of new-onset polyarthritis in patients with HS treated with infliximab appears to be specifically related to both the disease and the treatment. With the exception of case 5, which may be considered as serum sickness, the underlying mechanisms remain elusive and further studies are required to establish whether this novel clinical picture is specific for infliximab treatment or can also be observed with other TNF blockers and biologics.

REFERENCES

CHAPTER 8

Six patients with pyoderma gangrenosum successfully treated with infliximab

J.E. Mooij, D.C. van Rappard, J.R. Mekkes

International Journal of Dermatology 2013; 52: 1418-20
Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis, characterized by acute and progressive skin ulcers, usually located on the legs.¹

We report the results of six patients with PG who were treated with infliximab after they had not responded to conventional immunosuppressives. They received three infusions of infliximab 5 mg/kg at weeks 0, 2, and 6 and subsequently every 2 months, until all lesions were in remission. The diagnosis of PG was based on clinical and histological findings and was concluded after other pathology had been excluded. Underlying associated systemic disease was present in three patients (inflammatory bowel disease [IBD], n = 1; rheumatoid arthritis, n = 2). Two patients suffered from concomitant hidradenitis suppurativa. The patients’ mean age was 49 years (range: 21–77 years). The male : female ratio was 1 : 5. Lesions were located mainly on the legs. The average duration of disease before the initiation of infliximab was six years (range: 0.6–17.0 years).

The initiation of infliximab halted the progression of existing lesions; no new lesions developed, and all existing ulcers healed. Two patients were grafted with autologous skin grafts to accelerate wound healing (Fig. 1). Complete resolution of ulcers was achieved in a mean of 10.7 months (range: 3–24 months) after a mean of 8.2 infusions (range: 4–15 infusions). Treatment was discontinued in five patients, and no other immunosuppressive medications were required. One patient with coexisting IBD continued infliximab treatment. No recurrence of PG ulcers has yet been observed after a mean follow-up of 1.2 years. Temporary side effects were seen in two patients. One patient experienced erysipelas, which was treated easily with antibiotics. Another patient developed severe arthritis and myalgia. This patient was switched to another tumor necrosis factor-α (TNF-α) inhibitor (adalimumab), and disease activity was again controlled. Cultures taken from the ulcers mainly revealed *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and normal skin flora. The average cost of treatment (medication only) was €19,500 (US$28,082) per patient.

Pyoderma gangrenosum is a rare but serious skin disease first described in 1930 by Brunsting et al.² Its pathogenesis is unknown, but an immunological background has been suggested. In approximately 50% of patients, an underlying immunological disease is present. Rheumatoid arthritis, IBD, and hematological disorders are most commonly associated with PG. About 2% of IBD patients will develop a PG ulcer. In about 40% of PG patients, ulcers are idiopathic.¹ Two of the six patients described here also suffered from hidradenitis suppurativa, which is a rare but known association.³ Pyoderma gangrenosum and hidradenitis suppurativa are both associated with Crohn’s disease. About 1% and 0.00001% of the general population suffer from hidradenitis suppurativa and PG, respectively.⁴ As both conditions are neutrophilic dermatoses, a common immunological pathway is likely.

There is no consensus about the best treatment options for PG. Initially, an effort must be made to detect and control possible underlying systemic disease. Good local wound care is also important. Sometimes spontaneous healing occurs in weeks or months after onset, but often high doses of immunotherapy are required. Mild cases
with superficial ulceration may respond to local therapy with potent corticosteroid or tacrolimus ointment. The mainstay of systemic treatment is prednisone in doses of 0.5–1.0 mg/kg. In prolonged therapy, azathioprine or mesalazine can be added. In severe recalcitrant forms, and in patients in whom conventional treatments are contraindicated, anti-TNF-α treatment can be an option. TNF-α inhibitors are also effective in other immune diseases, especially the neutrophilic dermatoses. The first positive results of biologics in PG were described in patients with Crohn’s disease and associated PG. Infliximab is most frequently used, although adalimumab and etanercept also appear to be effective, as shown in one of our patients.

In conclusion, this report confirms that infliximab can be a very effective treatment in severe recalcitrant PG.
REFERENCES


CHAPTER 9

Mild to moderate hidradenitis suppurativa treated with local excision and primary closure

D.C. van Rappard, J.E. Mooij, J.R. Mekkes

Journal of the European Academy of Dermatology and Venereology 2012; 26: 898-902
ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic skin disease with a great impact on quality of life. Treatment with antibiotics or anti-inflammatory drugs, such as prednisone or TNF-alpha-inhibitors usually achieves only temporary improvement. Surgical intervention is considered as the only curative treatment for recurrent lesions.

Objective: To determine the efficacy and patient satisfaction of local excision followed by primary closure.

Methods: Between 2005 and 2010, 92 local excisions with primary closure were performed in 57 patients with mild to moderate HS. All patients were treated on an outpatient basis, under local anaesthesia. Local excision was defined as complete excision of the affected tissue, beyond the borders of activity, leaving clear margins. The medical records were reviewed retrospectively in 2010. The final outcome of the procedure, cosmetic appearance and patient satisfaction was measured using a questionnaire.

Results: Successful treatment, without recurrence, was accomplished in 66% of the cases. The intervention was generally well tolerated: 84% of the patients stated that they would undergo the same surgical procedure again if necessary, and 89% would recommend the procedure to other patients.

Conclusion: Local excision followed by primary closure is a valuable treatment for patients with mild to moderate HS (Hurly stage I & II), with low morbidity and a high patient satisfaction rate.
INTRODUCTION

Hidradenitis suppurativa (HS), also called acne inversa or ectopica, is a chronic, recurrent, debilitating skin disease. It is characterized by follicular hyperkeratosis followed by purulent inflammation of the pilosebaceous unit, leading to painful abscesses, scars and sinus tract formation. Most frequently affected are the apocrine gland-bearing areas of the body, such as the axillary, inguinal and anogenital regions. HS is not an uncommon disease with a prevalence rate of 1%, and women are more commonly affected than men. The invariably painful, unsightly lesions, accompanied by malodorous discharge and movement restriction, make HS a highly distressing condition with a significant impairment of quality of life.

The severity of HS can be assessed using the Hurley’s grading system, which separates three groups, mainly based on the presence and extent of cicatrization and sinuses. This grading system can be useful for general classification and may structure the basis for selection of the appropriate treatment.

Many conventional therapies, such as topical antibacterial or antiseptic lotions, systemic antibiotics, corticosteroids, retinoids and hormonal therapy have been described, often with limited or temporary results. More recently, the off-label use of anti-tumour necrosis factor alpha (TNF-alpha) biological agents in patients with severe HS has shown promising results with long-term efficacy. Nevertheless, also in these severe patients treated with TNF-inhibitors, surgical removal of all remaining sinuses is recommended as the crucial final step. In general, early referral for surgical intervention is recommended in all HS-patients, to limit the extent of this debilitating disease. Surgical treatment for HS may consist of a variety of methods (Table 1). This report describes our experiences with local excision followed by primary closure.

Table 1. Surgical options in hidradenitis suppurativa

<table>
<thead>
<tr>
<th>Surgical procedures</th>
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<tbody>
<tr>
<td>1. Incision and drainage</td>
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<tr>
<td>2. Deroofing</td>
</tr>
<tr>
<td>3. CO2 laser surgery</td>
</tr>
<tr>
<td>4. Excision</td>
</tr>
<tr>
<td>- Limited excision</td>
</tr>
<tr>
<td>- Wide excision with 1-3 cm margin into healthy tissue</td>
</tr>
<tr>
<td>- Excision of all hair-bearing skin (axilla)</td>
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<table>
<thead>
<tr>
<th>Wound closure techniques</th>
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</thead>
<tbody>
<tr>
<td>1. Primary closure</td>
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<tr>
<td>2. Secondary closure</td>
</tr>
<tr>
<td>- Split skin graft</td>
</tr>
<tr>
<td>- Local or distant flaps</td>
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<td>3. Healing by secondary intention</td>
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METHODS
In this retrospective single-centre study, the medical records of 57 consecutive HS-patients treated between 2005 and 2010 in the Department of Dermatology with local surgery and primary wound closure were analysed. All patients were treated on an outpatient basis, under local anaesthesia. Local excision was defined as complete excision of the affected tissue, beyond the borders of activity, leaving clear margins. The patients were informed in advance about the possible risks related to surgical procedures of non-sterile lesions, including the risk of infection, recurrence, dehiscence and unattractive scars.

Patients were suitable for local excision if: (i) they had recurrent abscesses or fistulas in the same location; (ii) if the excision could be performed with margins until healthy tissue around and below the lesion (Hurly stage I & II) and; (iii) their lesions were not larger than approximately hand palm size, because of the maximum amount of lidocaïne that could be used per procedure.

If the excisions were subsequently managed by primary closure, patients’ data were included in the study. Patients who had been treated with other surgical methods such as incisions, de-roofing procedures or wide excisions under general anaesthesia (Hurley stage III) were excluded. The immediate post-operative results were extracted from the medical records. For the long-term follow-up, all patients were contacted by telephone and/or letter and asked to fill out a questionnaire, at the end of 2010. For patients treated in 2005, this resulted in a 5-year interval between their first surgical intervention and evaluation. The minimal interval between surgery and evaluation had to be at least 3 months. The questionnaire included general questions on disease duration, smoking habits and previous treatments. Pain during the procedure was recorded using a pain score ranging from 0 to 10. The clinical course was evaluated by asking questions on post surgical pain, occurrence of complications, time required for resuming daily activities, time required for total wound healing and recurrence rate. In addition, the patients had to give an overall judgment of cosmetic results of the postoperative sites. Finally, patients were asked if they would have surgery again if necessary and if they would recommend similar procedures to other patients with comparable conditions.

RESULTS
In total 92 excisions followed by primary closure were performed in 57 patients (47 women and 10 men). The average age was 42.5 years (range 20–62). Average duration of disease before active surgical intervention was 13.6 years (range 1.5–35). Ninety one percent of the patients smoked or had been smoking in the past. All but two patients had used conventional medical therapies before deciding to have surgery. The disease primarily involved the inguinal-genital region (46 sites) followed by the axillary region (34 sites) and the perianal region (8 sites). Other effected sites included
the sub-mammary region, the upper leg and lower abdomen. Patient characteristics and results are summarized in Table 2 and 3. The follow-up period ranged from 3 months to a maximum of 84 months (average 14 months).

Clinical course
Postoperative pain, requiring pain medication, was present after 61% of the surgical interventions. The average duration for patients for resuming daily activities was 1.5 weeks. The average time required for total wound healing was 3.2 weeks. The overall rate of postoperative complications was 29%, mostly minor complications like suture dehiscence, postoperative bleeding and postoperative infection. In none of the cases, hospitalization was required.

Recurrence
Successful treatment, without any recurrence, was accomplished in 66% of the cases (Figs. 1 and 2). The average follow-up duration without recurrence was 27 months. Recurrence within the operated fields occurred in 23% of the cases, after an average duration of 10 months. In 11% of the cases, de novo suppurating lesions appeared near the initial sites of surgery, after an average duration of 5 months.

Patient satisfaction
The surgical procedure and clinical course were well tolerated and patients were generally satisfied. Most patients regarded surgery as the only consistently effective therapy. The surgical procedure was graded by the patients with an average pain score of 3.2 on a 10 point scale. Forty-eight patients (84%) declared that they would undergo the same surgical procedure again if necessary. Fifty-one patients (89%) would recommend similar procedures to others with comparable conditions.

Cosmetic appearance
Patients rated the cosmetic results reasonable or good in 83% of the cases, with male patients, and older patients being less critical on the final result. The remaining 17% considered the cosmetic appearance as poor. Nevertheless, some of them declared that although the cosmetic results were not good, the lesions present before surgery were much worse.

Discussion
The conclusion from this retrospective study is that local excision, followed by primary closure is a valuable treatment for patients with mild to moderate HS. It is a safe way of disease control, with low morbidity, rapid wound healing and a high patient satisfaction rate. Most patients (89%) tolerated the procedure well and would
recommend it to other patients. This satisfaction rate is in accordance with previous literature describing surgical methods for HS.10–12 As recurrence of lesions within the operated field occurred in 23%, the patient satisfaction was better than expected. An explanation for this discrepancy is that patients benefit from surgery anyway, even if relief is temporary or partial. In the cases where lesions recurred, they often developed to a lesser extent than before. Recurrence of lesions near the operated field (11%) may be new lesions or hidden fistulas, not sufficiently removed during the first excision. Patients who develop recurrent lesions can be re-operated easily using the same technique or other procedures such as deroofing or wide excision.

The pain scores of the surgical procedure showed a wide variation, ranging from 0 to 10. In all cases, the injection of local anaesthetics was responsible for the pain. Some patients rated the pain with 10 and described the injection of lidocaïne in the already inflamed, sensitive tissue as the worst imaginable pain. Other patients rated
Table 2. Summary of patient characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Male</td>
<td>10  (18%)</td>
</tr>
<tr>
<td>- Female</td>
<td>47  (82%)</td>
</tr>
<tr>
<td>- Smoking</td>
<td>52  (91%)</td>
</tr>
<tr>
<td>Average duration of disease (years)</td>
<td>13.6</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>42.5</td>
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Number of surgical procedures 92

<table>
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<th>Areas of involvement</th>
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<tbody>
<tr>
<td>- Inguinal-genital</td>
<td>46  (50%)</td>
</tr>
<tr>
<td>- Axillae</td>
<td>34  (37%)</td>
</tr>
<tr>
<td>- Perianal</td>
<td>8   (9%)</td>
</tr>
<tr>
<td>- Other</td>
<td>4   (4%)</td>
</tr>
</tbody>
</table>

Figure 3. Deroofing procedure: (a) marking the affected area (b) removal of the ‘roofs’ of sinus tracts and leaving the major part of the epithelium covering the floor of the abscess in situ. (c, d) From this epithelial source, rapid healing within 2–3 weeks takes place.
the pain with a zero, and explained that the pain was negligible compared with their usual chronic pain caused by recurrent inflamed abscesses.

Not surprisingly, 91% of the patients smoked or had been smoking in the past, as HS is strongly correlated with cigarette smoking. A direct correlation between disease severity of HS and smoking habits is present.13 Two female patients, with genital and perianal lesions, were of exceptional young age at the time of disease onset (13 years), and did not have a history of smoking. In both cases, a family history of severe HS was present. A familial predisposition for HS has been described before.14

Although patients with chronic HS often benefit from long-term use of antibiotics, there is no evidence that treatment other than surgery can cure the condition.9,11,15 Referral for surgical intervention as early as possible is strongly recommended. Regrettably, in most cases, it takes years before curative operative treatment is initiated.16 Also, in our study the average time between first onset and surgical intervention was long (13.6 years).

Table 3. Outcome of the patient questionnaire

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score (0-10)</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post operative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post operative pain</td>
<td>56 (61%)</td>
</tr>
<tr>
<td>Time to resume daily activities (wk)</td>
<td>1.5</td>
</tr>
<tr>
<td>Time until total wound healing (wk)</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>65 (71%)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>20 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence</td>
<td>61 (66%)</td>
</tr>
<tr>
<td>Recurrence same site</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>Recurrence near operation site</td>
<td>10 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Satisfaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetic results</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>34 (37%)</td>
</tr>
<tr>
<td>Reasonable</td>
<td>42 (46%)</td>
</tr>
<tr>
<td>Poor</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Recommendation</td>
<td></td>
</tr>
<tr>
<td>Would have surgery again</td>
<td>48/57 (84%)</td>
</tr>
<tr>
<td>Would recommend it to others</td>
<td>51/57 (89%)</td>
</tr>
</tbody>
</table>
Various surgical techniques are used in HS-patients, such as incision and drainage, deroofing, CO₂ laser surgery and excision followed by various wound closure methods. Incision and drainage offer only temporary relief. Deroofing (Fig. 3) consists of removal of the ‘roofs’ of sinus tracts with preservation of the bottom of the tracts, which leads to fast re-epithelialization. A comparable result can be achieved using carbon dioxide laser treatment.

The mainstay of surgical management remains complete excision of affected tissue leaving clear margins. Inadequate excision of diseased tissue is the major cause of recurrence.

No consensus exists on the ideal extent of the margins. Our study suggests that limited excision can be used in ‘mild’ cases with well-defined small to medium-size lesions, separated by healthy tissue (Hurley stage I). In more severe cases, when sinus tract formation is present (Hurley stage II) or in case of interconnected tracts (Hurley stage III), most authors recommend a wider margin of 1–3 cm into healthy tissue, and in axillary lesions total removal of all hair-bearing tissue may be considered.

Another point of disagreement concerns the choice of wound closure. Excision followed by primary closure is generally used for localized disease, clearly because for larger defects, primary closure cannot be achieved. This method has proven to be successful, and is preferred by many patients because of faster healing, less postoperative pain and no necessity of daily dressing changes. On the other hand, many specialists have criticized this method, and claim that attempts to obtain primary skin closure may lead to inadvertent compromise of the excision margin, increasing the risk for recurrence.

Larger defects, resulting from wide excisions, can either be covered with flaps or skin grafts or left open to heal by secondary intention. The majority of studies advocated healing by secondary intention noticed low recurrence rates. A disadvantage of healing by secondary intention is the long duration (4–12 weeks) of the healing process.

The extent of the margin of the surgical excision has the largest influence on the recurrence rates. Other factors such as the patient’s co-morbidity, the experience of the surgeon and the anatomical location of the lesions influence recurrence rates as well. Recurrence occurs more often in the inguinal and sub-mammary regions, compared with the axillary and perianal regions. Also, shorter disease duration and a smaller amount of areas affected by disease, indicating a lower disease severity, predict a better surgical outcome.

In conclusion, the published data on effectiveness of surgery and different wound closure techniques do not provide a uniform solution that can be applied to all patients. The selection of the appropriate technique, excision size and closure technique depends on the extent of skin and soft-tissue involvement. For patients with mild to moderate HS, local excision followed by primary closure can be a valuable treatment, with low morbidity and a high patient satisfaction rate. The excision can be performed on an outpatient basis under local anaesthesia (office surgery), which is another advantage because expensive and scarce operating room facilities can be saved and used for more complex procedures.
REFERENCES

CHAPTER 10

Treatment of severe hidradenitis suppurativa with infliximab in combination with surgical interventions

D.C. van Rappard, J.R. Mekkes

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Hidradenitis suppurativa (HS) is a chronic recurrent skin disease characterized by painful abscesses, scars and sinus tract formation. Current treatment modalities such as topical antibacterial lotions, systemic antibiotics and corticosteroids achieve only temporary improvement.\textsuperscript{1,2} Recently, treatment with the tumour necrosis factor (TNF)-\(\alpha\) inhibitors infliximab and adalimumab has shown promising results in patients with severe HS.\textsuperscript{3–6} Still, many authors claim that surgical intervention is the only effective treatment to cure the condition.\textsuperscript{7,8}

Based on the experiences of recent years, it became common practice in our hospital to treat patients with severe recalcitrant HS with a multifactorial approach, as was recently described in the Dutch treatment guidelines for HS.\textsuperscript{9} The first step is treatment with two antibiotics (clindamycin 300 mg twice daily + rifampicin 300 mg twice daily) for 2–4 months. If patients are not responding to antibiotic treatment, and a clear inflammatory component [purple inflammation around HS lesions, rubor, calor, dolor, fever, increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] is present, a TNF-\(\alpha\) inhibitor is added. Subsequently, after an observation period of 3–6 months, remaining sinuses and fistulas not responding to the anti-inflammatory treatment are removed surgically.

In a retrospective study we analysed the medical records of 30 patients treated with infliximab in our hospital between 2000 and 2010. The characteristics of all patients, including data on surgical procedures, were collected. Clinical efficacy was evaluated using laboratory parameters, such as ESR and CRP. In addition, a physician global assessment (PGA), consisting of a four-point scale (1, no improvement; 2, moderate improvement; 3, improvement; 4, free of lesions), was used. The PGA scores, compared with baseline, were assessed at three separate times: after treatment with infliximab, after additional surgical treatment, and at the end of the follow-up period.

Thirty patients (17 men and 13 women) were included in the study. Most patients (\(n = 26; 87\%\)) had Hurley grade III HS; four patients (13\%) had Hurley grade II.\textsuperscript{10} The mean disease duration was 17 years (range 4–35). The mean age was 44 years (range 19–63), and 29 patients (97\%) were cigarette smokers. Five patients (17\%) were obese (> 100 kg). In 24 patients (80\%) infliximab treatment was followed by surgery to remove remaining fistulas or sinuses. Six patients (20\%) were treated with infliximab only and improved remarkably. In four of them additional surgery was not necessary. Two patients declined further surgical treatments for personal reasons. The number of infusions ranged from 2 to 24, correlating with a mean treatment duration of 9.3 months (range 0.5–40), starting with infusions at weeks 0, 2 and 6 and subsequently every 8 weeks. Patients were followed for a mean of 50 months (maximum 127 months).

The inflammatory parameters ESR and the CRP improved significantly after treatment with infliximab (Fig. 1a). The mean ESR was reduced from 52 to 23 mm in the first hour and the mean CRP was reduced from 37.7 to 11.3 mg L\(^{-1}\) (\(P < 0.001\)).

Infliximab reduced the overall disease activity, particularly the inflammatory component. Large fistulas and cavities that were already epithelialized did not disappear under infliximab treatment and had to be removed surgically. Twenty-four patients were
Figure 1. (a) Mean reduction of erythrocyte sedimentation rate (ESR; mm in the first hour) and C-reactive protein (CRP; mg L$^{-1}$) before and after treatment with infliximab, in 30 patients ($P < 0.001$). (b) Percentage of patients improved or healed following infliximab treatment. (c) Percentage of patients improved or healed following infliximab + surgery. HS, hidradenitis suppurativa.
treated with a combined treatment approach including surgical interventions (mean 2.8 interventions per patient) such as deroofing procedures and small to large excisions, followed by healing by secondary intention, primary closure or grafting procedures.

The PGA performed after the infliximab treatment period showed that one patient (3%) did not improve at all, seven patients (23%) were moderately improved, 18 patients (60%) were improved, and four patients (13%) became free of lesions. This resulted in a mean PGA of 2.8 (Fig. 1b). The second PGA was performed after all additional surgical interventions were done. Three patients (10%) showed moderate improvement, 16 patients (53%) improved, and 11 patients (37%) became free of lesions (Fig. 1c). This multistep treatment resulted in a mean PGA of 3.3, which was significantly better than the PGA observed after infliximab treatment alone ($P < 0.001$). The third PGA was performed at the end of the follow-up period. With the combination of infliximab and additional surgery, 10 of the 30 patients were still free of lesions (33%) (Fig. 2). They are currently not taking any medication and they are considered as healed. Thirteen patients (43%) are still improved, four patients (13%) moderately improved, and three patients (10%) still have severe HS.

Figure 2. Hidradenitis suppurativa of the buttocks. (a) Initial situation with inflamed painful lesions and pus-draining fistulas. (b) Control of the inflammatory component after treatment with infliximab. Some nodules and fistulas have healed completely. (c) Excision of a remaining fistula. (d) The patient is still free of complaints: no recurrence of symptoms during a follow-up period of 6 years.
Adverse events due to infliximab treatment were observed in 12 of 30 patients, resulting in discontinuation of treatment in nine of them. Complications of surgery during or shortly after treatment with infliximab were not observed.

Despite the limitations of the retrospective study design, the data suggest that infliximab can be an effective treatment for patients with severe recalcitrant HS, and that the healing rate can be further increased by combining TNF-α inhibitors with subsequent surgical removal of remaining lesions. We recommend a combined approach consisting of antibiotics, TNF-blockers, and surgery in severe cases.

REFERENCES

CHAPTER 11

Summary and conclusions
Samenvatting en conclusies
SUMMARY AND CONCLUSIONS: BIOLOGICAL AND SURGICAL TREATMENT OF SEVERE HIDRADENITIS SUPPURATIVA

In this thesis, we discuss the biological and surgical treatment options for severe hidradenitis suppurativa (HS). A minor part of this thesis covers the disease’s genetic background and provides new insights into the clinical description of HS.

The general introduction in Chapter 1 provides a complete overview of HS. It summarizes the existing knowledge of its etiology, pathogenesis, clinical and histological features, and the current treatment modalities.

In Chapter 2 we describe a systematic search which we performed to identify all randomized controlled trials (RCTs) for the treatment of HS, in order to systematically review and critically evaluate currently available evidence. A systematic search was undertaken in the electronic databases up to January 30th 2015. Eleven RCTs were selected and critically appraised. Four studies involved biological therapy with anti-tumor necrosis factor-alpha (anti-TNF-α). Two studies investigated the role of antibiotics and one study investigated hormonal therapy. We also included three studies on laser therapy, and one study of surgical management. Based on the available evidence, the following therapies can be used to improve HS: topical clindamycin, oral tetracycline, anti-androgens, adalimumab, infliximab, the intense pulsed light, the Nd:YAG laser, and an additional gentamicin-collagen sponge after surgery. The use of etanercept is discouraged. We conclude that there is variety of treatment modalities available for HS, but most of them lack high quality evidence. Due to the scarce amount of RCTs it is not possible to base implications for daily practice solely on high level evidence. Also, this systematic review emphasizes the need for the use of validated and uniform outcomes, in order to facilitate indirect comparison of available treatments and to promote evidence-based clinical practice.

In Chapter 3 we examine our hypothesis that polymorphisms in the CARD15/NOD2 gene, as expressed in Blau Syndrome and Crohn’s disease, may have a comparable role in HS. We analyzed the entire coding region of the CARD15/NOD2 gene in six patients with a high ‘pre-test probability’ of having a genetic factor. The patients were separated in three categories: two patients with HS and coexisting pyoderma gangrenosum; two patients with HS, coexisting pyoderma gangrenosum, and additionally (cutaneous) Crohn’s disease, and; two patients with a pre-pubertal HS onset and a positive family history of severe HS. In none of the six patients a mutation of the CARD15/NOD2 could be detected. As these patients, in light of their high risk-profiles, were highly suspected to express the CARD15/NOD2 mutation, it seems unlikely that this mutation will be found in other patients with HS.

Chapter 4 adds a new perspective to our current knowledge of the clinical features of HS. In a large series of 596 HS patients, we noticed that four patients had an atypical clinical presentation, consisting of superficial slowly migrating inflammatory...
plaques with a strikingly cribriform pattern. These plaques developed in different body areas (arm, leg, thigh, abdomen), and partly resembled pyoderma gangrenosum. Histopathology showed characteristics compatible with the diagnosis of HS. We conclude that this is a rare clinical subform and suggest the name “plaque form HS” for this entity. Due to the rarity of the disease, a recommendation for treatment can only be based on our own limited experience. Treatment consisted of anti-inflammatory medication, followed by surgical treatment, leading to disease control.

The efficacy and safety of infliximab and adalimumab are evaluated in Chapter 5 by comparing two cohorts of 10 patients suffering from severe, recalcitrant HS. Ten patients were treated with infliximab i.v. (3 infusions of 5 mg/kg at weeks 0, 2, and 6). Several years later 10 other patients were treated in the same hospital with adalimumab s.c. 40 mg every other week. Both cohorts were followed up for 1 year, using identical evaluation methods, including the Sartorius score. Eventually, a total of 19 patients completed the study, and in both groups the severity of the HS diminished. Nevertheless, infliximab performed better in all aspects. The average Sartorius score was reduced to 54% of baseline for the infliximab group and to 66% of baseline for the adalimumab group. Based on these data we conclude that adalimumab s.c. 40 mg every other week is less effective than infliximab i.v. 5 mg/kg at weeks 0, 2, and 6.

In the absence of a consensus on which biological is best suited for the treatment of HS, we performed a systematic review which we describe in Chapter 6. We provide an overview of the current evidence regarding off-label treatment of HS with TNF-α inhibitors. Any type of original article concerning HS patients treated with infliximab, etanercept and/or adalimumab was included. After full-text screening 65 studies (involving 459 patients) met the inclusion criteria, and were subjected to data extraction. The 65 selected studies included four RCTs. All others were case series or reports. The efficacy data extracted from the case reports showed a moderate-to-good response in 82% of patients treated with infliximab, in 76% of patients treated with adalimumab, and in 68% of patients treated with etanercept. Based on the combination of RCTs and of the case series and reports, we conclude that, if conventional treatment options fail, the use TNF-α inhibitors can be a useful supplement for the treatment of recurrent severe HS. Infliximab should be preferred based on the most encouraging results regarding efficacy and expenses, and adalimumab seems promising when administered in higher doses. We discourage the use of etanercept.

In Chapter 7 we describe a new observation that some HS patients develop arthritis after treatment with infliximab. We retrospectively observed that 5 of the 27 HS patients (18.5%) who were treated with infliximab developed an acute and painful polyarthritis during treatment. The arthritis occurred on average after 12 months of treatment, was not clearly associated with anti-infliximab antibodies, and resolved after an average of 4 months. Interestingly, none of the patients had suffered from arthritis before, despite the long duration of HS and the fact that all showed a good skin response to infliximab. We compared the frequency of arthritis to that of control groups consisting of 227 HS patients who were not treated with infliximab.
patients not treated with any biological, 22 HS patients treated with adalimumab and 28 patients with psoriasis treated with infliximab, in the same period and same clinic. Noticeably, arthritis was not observed in any of the control groups. Compared to the adalimumab group and the psoriasis group, an odds ratio of 7.241 (95% CI 1.15 to 45.6) and 9.025 (95% CI 1.45 to 55) were calculated. Based on these five cases we suggest that infliximab treatment in HS can induce a transient but severe polyarthritis, but that the underlying mechanisms remain to be further investigated.

In Chapter 8 we widen our view on off-label indications for treatment with biologicals. We report six patients with severe recalcitrant pyoderma gangrenosum, who were treated with infliximab. Two patients had concomitant HS. Patients received 3 infusions of 5 mg/kg at weeks 0, 2, 6 and subsequently every 2 months, until all lesions were in remission. On average, total healing was achieved in 10.7 months, after 8.2 infusions. Treatment was discontinued in five patients, and continued in one patient with coexisting inflammatory bowel disease. We observed no recurrence of pyoderma gangrenosum ulcers after a mean follow-up duration of 1.2 year. Therefore this report supports the perception that infliximab can also be very effective for treating severe recalcitrant pyoderma gangrenosum.

In Chapter 9 we focus on the use of surgery for HS. We present the efficacy and patient satisfaction of 57 patients with mild to moderate HS, who were treated between 2005 and 2010 with local excisions and primary closure. We retrospectively reviewed their medical records. A total of 92 local excisions followed by primary closure was performed. The results show that successful treatment, without recurrence, was accomplished in 66% of the cases. The intervention was generally well tolerated: 84% of the patients stated that they would undergo the same surgical procedure again if necessary and 89% would recommend the procedure to other patients. Therefore we conclude that local excision followed by primary closure is a valuable treatment for patients with mild to moderate HS, with low morbidity and a high patient satisfaction rate.

In our final chapter, Chapter 10, we make the connection between the treatment of HS based on biologicals and the treatment based on surgery. We retrospectively studied the medical records of 30 patients, who were treated with infliximab between 2000 and 2010. Patients’ characteristics and data on additional surgical procedures were collected. Six patients were treated with infliximab alone and in 24 patients infliximab was followed by surgical interventions. After infliximab treatment alone, 18 patients (60%) improved, and 4 patients (13%) became free of lesions, resulting in an average physician global assessment (PGA) of 2.8. After additional surgical interventions 16 patients (53%) improved, and 11 patients (37%) became free of lesions, resulting in a significantly higher average PGA of 3.3 (p<0.001). After an average follow-up period of 50 months 33% of the patients was still free of lesions. We conclude that the combined approach of infliximab followed by surgical intervention is an effective treatment strategy for patients with severe HS and should be preferred to infliximab alone.
SAMENVATTING EN CONCLUSIES: DE BEHANDELING VAN ERNSTIGE HIDRADENITIS SUPPURATIVA MET BIOLOGICALS EN CHIRURGIE

In dit proefschrift bediscussiëren we de behandelopties voor ernstige hidradenitis suppurativa (HS). We richten ons met name op de biologicals en de chirurgische interventies. Een klein deel van dit proefschrift gaat over de genetische achtergrond en geeft daarnaast nieuwe inzichten in het klinische beeld van HS.

De algemene inleiding in Hoofdstuk 1 geeft een compleet overzicht van HS. De bestaande kennis met betrekking tot de etiologie, pathogenese, klinische en histologische kenmerken, en de huidige behandelmogelijkheden worden samengevat.

In Hoofdstuk 2 beschrijven we onze systematische review van alle gerandomiseerde gecontroleerde studies (RCTs) die over de behandeling van HS gaan. Op die manier hebben we de huidige evidence op dit gebied kunnen onderwerpen aan nauwkeurig onderzoek en kritische evaluatie. Een systematische zoekactie werd uitgevoerd in de elektronische databases tot aan 30 januari 2015. Elf RCTs werden geselecteerd en kritisch beoordeeld. Vier van die studies gingen over therapie met anti-tumor necrosis factor-alpha (anti-TNF-α) biologicals. In twee studies werd de rol van antibiotica onderzocht en in één studie de rol van hormoonbehandeling. Daarnaast werden ook drie studies over laserbehandeling en één studie over de chirurgische management geïncludeerd. Afgaand op de bestaande evidence concluderen we dat de volgende therapieën ingezet kunnen worden bij de behandeling van HS: clindamycine topicaal, tetracycline oraal, anti-androgenen, adalimumab, infliximab, de intense pulsed light, de Nd:YAG laser en een additionele gentamicine-collageenspons na chirurgie. Het gebruik van etanercept wordt afgeraden. We concluderen dat er een variëteit aan behandelopties beschikbaar is voor HS, maar dat onderbouwing door hoge kwaliteit evidence vaak ontbreekt. Door de beperkte hoeveelheid RCTs, is het niet mogelijk om de dagelijkse praktijkvoering enkel te baseren op hoge kwaliteit evidence. Daarnaast wordt in dit systematische review de behoefte aan het gebruik van gevalideerde en uniforme uitkomstparameters benadrukt, om indirecte vergelijking van de beschikbare behandelopties mogelijk te maken en om evidence-based praktijkvoering te bevorderen.

In Hoofdstuk 3 onderzoeken we onze hypothese of een polymorfisme in het CARD15/NOD2 gen een rol speelt bij HS, net zoals dat het geval is bij het Blau syndroom en de ziekte van Crohn. We hebben de gehele coderingsregio geanalyseerd van het CARD15/NOD2 gen bij zes patiënten met een hoge verdenking op het hebben van een genetische factor. De patiënten werden verdeeld in drie categorieën: twee patiënten met HS en bestaande pyoderma gangrenosum; twee patiënten met HS, bestaande pyoderma gangrenosum en bijkomend de ziekte van (cutane) Crohn; twee patiënten die HS ontwikkelden voor hun puberteit en met een positieve familieanamnese van ernstige HS. In geen van deze zes patiënten kon een mutatie in het CARD15/NOD2 worden gedetecteerd. Omdat deze patiënten door hun hoge risicoprofiel zeer verdacht
waren voor het hebben van een mutatie in het CARD15/NOD2, lijkt het onwaarschijnlijk dat deze mutatie in andere patiënten met HS gevonden zal worden.

**Hoofdstuk 4** voegt nieuwe perspectieven toe aan onze huidige kennis over het klinisch beeld van HS. In een grote groep van 596 patiënten, sprongen er vier patiënten uit met een atypisch klinisch beeld, bestaande uit oppervlakkige, langzaam uitbreidende, inflammatoire plaques met een opmerkelijk cribriform patroon. Deze plaques werden waargenomen op verschillende delen van het lichaam (arm, been, dij, abdomen) en hadden deels iets weg van pyoderma gangrenosum. Het histopathologisch beeld paste goed bij de diagnose van HS. Wij concluderen dat het hier gaat om een zeldzame klinische variant, en opperen de naam “plaque form HS” voor deze entiteit. Omdat deze aandoening zo sporadisch optreedt, is het advies voor de behandeling alleen gebaseerd op onze eigen beperkte ervaring. De behandeling bestond uit anti-inflammatoire medicatie, gevolgd door chirurgisch ingrijpen, wat uiteindelijk leidde tot genezing.

De effectiviteit en veiligheid van infliximab en adalimumab worden beoordeeld in **Hoofdstuk 5** op basis van een vergelijking van 2 cohorten van 10 patiënten met ernstige, hardnekkige HS. Tien patiënten werden behandeld met infliximab i.v. (3 infusies van 5 mg/kg op week 0, 2 en 6). Enkele jaren later werden 10 andere patiënten behandeld in hetzelfde ziekenhuis, ditmaal met adalimumab s.c. 40 mg om de week. Beide cohorten werden gedurende 1 jaar gevolgd en volgens identieke methodes geëvalueerd, waaronder de Sartorius score. Uiteindelijk volbrachten 19 patiënten de studie. In beide groepen nam de ernst van HS af, maar Infliximab deed het beter op alle fronten. De gemiddelde Sartorius score werd gereduceerd tot 54% in de infliximab groep en tot 66% in de adalimumab groep, gerekend vanaf baseline. Gebaseerd op deze data concluderen wij dat adalimumab s.c. 40 mg om de week minder effectief is dan infliximab i.v. 5 mg/kg op week 0, 2 en 6.

Omdat er geen consensus is over welke biological nu het meest geschikt is voor de behandeling van HS, werd een systematisch literatuuronderzoek uitgevoerd, waarvan verslag wordt gedaan in **Hoofdstuk 6**. We geven een overzicht van de huidige evidence met betrekking tot de off-label behandeling van HS met TNF-α remmers. Elk type studie van originele bron, betreffende patiënten met HS die werden behandeld met infliximab, etanercept en/of adalimumab, werd geïncludeerd. Na het screenen van de volledige tekst voldeden 65 studies (bestaande uit 459 patiënten) aan de inclusiecriteria. Deze studies werden onderworpen aan data-extractie. Onder de 65 studies waren vier RCTs. De overige studies waren case series of reports. De effectiviteitsdata die uit de case reports konden worden gehaald lieten een matig tot goede uitkomst zien in: 82% van de patiënten die werden behandeld met infliximab, in 76% van de patiënten die werden behandeld met adalimumab en in 68% van de patiënten die werden behandeld met etanercept. Gebaseerd op de gegevens uit de case reports en series, gecombineerd met de resultaten van de RCTs, concluderen we dat indien conventionele behandelingen onvoldoende effectief zijn, het gebruik van TNF-α remmers een waardevolle toevoeging kan zijn bij de behandeling van ernstige, recidiverende HS. Gebaseerd op de meest
aanmoedigende resultaten en het financiële aspect zou de voorkeur uit moeten gaan naar infliximab. Voorts lijkt adalimumab veelbelovend wanneer het wordt toegediend in hogere doseringen. Het gebruik van etanercept wordt afgeraden.

In Hoofdstuk 7 wordt een nieuwe observatie beschreven waarbij sommige HS patiënten artritis ontwikkelden na behandeling met infliximab. In een retrospectief onderzoek, stelden we vast dat 5 van de 27 HS patiënten (18.5%) die werden behandeld met infliximab, een acute en pijnlijke polyartritis ontwikkelden. Deze artritisklachten ontstonden na gemiddeld 12 maanden behandeling, verdwenen na gemiddeld 4 maanden, en waren niet duidelijk geassocieerd met anti-infliximab antistoffen. Opmerkelijk was het gegeven dat geen van de patiënten eerder artritisklachten had gehad, ondanks reeds lang bestaande HS, en dat ze allen goed reageerden op infliximab. We vergeleken de frequentie van artritis met dat van controlesgroepen bestaande uit 227 HS patiënten die niet werden behandeld met een biological, 22 HS patiënten die werden behandeld met adalimumab en 28 patiënten met psoriasis die werden behandeld met infliximab, in dezelfde periode in hetzelfde ziekenhuis. Opvallend genoeg werden geen observaties van artritis gedaan in de controlegroepen. Vergeleken met de adalimumab groep en de psoriasis groep kon een odds ratio van 7.241 (95% CI 1.15 to 45.6) en 9.025 (95% CI 1.45 to 55) worden berekend. Gebaseerd op deze vijf casus suggereren we dat de behandeling van HS met infliximab een tijdelijke maar ernstige polyartritis kan induceren, maar dat het onderliggende mechanisme hiervan in de toekomst verder onderzocht zou moeten worden.

In Hoofdstuk 8 verbreden we onze visie op de off-label indicaties voor behandeling met biologicals. We beschrijven zes patiënten met Ernstige, hardnekkige pyoderma gangrenosum, die werden behandeld met infliximab. Twee patiënten hadden bijkomend HS. De patiënten kregen 3 infusies van 5 mg/kg op week 0, 2, 6 en daarna iedere 2 maanden, totdat alle laesies verdwenen waren. Gemiddeld genomen werd genezing bereikt na 10.7 maanden, na 8.2 infusies. Behandeling werd gediscontinueerd bij vijf patiënten en gecontinueerd bij één patiënt met een reeds bestaande inflammatoire darmziekte. Er werd geen recidief gezien van de pyoderma gangrenosum ulcera, na een gemiddelde follow-up duur van 1.2 jaar. Derhalve ondersteunt dit artikel de perceptie dat infliximab ook zeer effectief kan zijn in de behandeling van ernstige, hardnekkige pyoderma gangrenosum.

In Hoofdstuk 9 ligt de nadruk op het toepassen van chirurgie bij HS. We presenteren de effectiviteit en patiënttevredenheid van 57 patiënten met milde tot matige HS, die tussen 2005 en 2010 werden behandeld met lokale excisie gevolgd door primaire sluiting van de wond. Al hun medische dossiers werden retrospectief bekeken. In het totaal werden 92 lokale excisies gevolgd door primaire sluiting uitgevoerd. De resultaten laten zien dat succesvolle behandeling zonder recidief werd behaald in 66% van de gevallen. De interventie werd over het algemeen goed getolereerd: 84% van de patiënten verklaarde dat ze dezelfde chirurgische procedure opnieuw zouden willen ondergaan indien nodig en 89% zou deze procedure aanraden aan andere
patiënten. Hieruit concluderen we dat lokale excisie gevolgd door primaire sluiting een waardevolle behandeling is voor patiënten met milde tot matige HS, met een lage morbiditeit en een hoge patiënttevredenheid.

In ons laatste hoofdstuk, Hoofdstuk 10, leggen we de verbinding tussen de behandeling van HS met biologicals enerzijds en de behandeling van HS met chirurgie anderzijds. We hebben retrospectief de medische dossiers van 30 patiënten bestudeerd, die tussen 2000 en 2010 werden behandeld met infliximab. De patiëntkarakteristieken en de gegevens met betrekking tot de aanvullende chirurgische ingrepen werden verzameld. Zes patiënten werden alleen met infliximab behandeld en bij 24 patiënten werd de infliximab behandeling gevolgd door chirurgische interventies. Na de behandeling met infliximab alleen verbeterden 18 patiënten (60%) en waren 4 patiënten (13%) geheel vrij van laesies. Dit resulteerde in een gemiddelde physician global assessment (PGA) score van 2.8. Na aanvullende chirurgische interventies verbeterden 16 patiënten (53%) en waren 11 patiënten (37%) geheel vrij van laesies. Dit resulteerde in een significant hogere gemiddelde PGA van 3.3 (p<0.001). Na een gemiddelde follow-up duur van 50 maanden was 33% van de patiënten nog steeds geheel vrij van laesies. We concluderen dat de gecombineerde benadering, bestaande uit infliximab gevolgd door chirurgische interventies, een effectieve behandelstrategie is voor patiënten met ernstige HS. Dit zou de voorkeur moeten hebben boven behandeling met infliximab alleen.
Clinical presentation

Hidradenitis suppurativa (HS) is a chronic purulent recurrent skin disease that affects approximately 1% of the general population. HS typically affects the flexural areas of the body such as the axilla, groin, submammary and perianal areas. Atypical locations, such as the retroauricular folds, neck and periumbilical region, are occasionally reported. The recent observation of a rare clinical variant, called ‘plaque form hidradenitis’, that may occur on all parts of the body, adds new perspectives to our current knowledge of the clinical features of HS. A multifactorial etiology has been assumed, including smoking, obesity, mechanical stress, immune dysregulation and a role for genetic alterations. HS is associated with a variety of other (skin) diseases, for instance: the follicular occlusion triad, pyoderma gangrenosum, squamous cell carcinoma, Crohn’s disease, spondyloarthopathies and metabolic syndrome.

Treatment guidelines

A diversity of treatment options is available for HS, including topical and systemic agents, as well as surgical interventions. In 2015, a new European S1 guideline for the treatment of HS was published. This guideline, composed by an expert group, is based on the currently available evidence, and proposes a treatment algorithm based on the Hurley severity grades. It may be helpful to create more uniformity in the treatment of HS.

Increased attention for HS

Although HS occurs rather commonly and has a great impact on patients’ lives, it has been relatively neglected over the last century in terms of research. It was only over the last decade that significant research attention for this devastating skin disease has been developing, as can be noticed from the rapidly expanding number of scientific publications on the subject. This can be partly explained by the high degree of attention for the recently introduced anti-TNF-α biologicals, which are applied as a last resort for treatment of recalcitrant HS. The promising results from several smaller and a few well-conducted large trials offer optimism for patients and physicians, since HS is generally perceived as a skin disease that is difficult to treat.

Randomized controlled trials

Four out of the 11 randomized controlled trials (RCTs) related to the treatment of HS that have been realized to date involve biological therapy with anti-TNF-α. This is not surprising, because large randomized trials are expensive to perform, and are generally sponsored by the pharmaceutical industry for registration purposes. The fact that more than one third of the RCTs involve biological therapy gives an unfair reflection of the commonly used treatment modalities for HS. Dozens of treatment options are available for the different severity stages of HS, and the use of biologicals is never considered to be the first step. Several well-established and crucial treatment options like antibiotics...
and other anti-inflammatory agents have, despite their wide use, never been properly investigated by means of randomized controlled prospective studies. Expensive and time-consuming investigator-initiated studies on this subject are obviously lacking. Therefore, implications for daily practice cannot be solely based on high-level evidence, but need to take into account findings from less profound research as well.

**Surgical interventions**

RCTs that focus on surgical interventions are absent, probably because it is considered unethical to deny the control group access to surgical treatment for a prolonged period of time, or because of the fact that it is simply not possible to create a placebo group. The results of surgery are usually described in prospective or retrospective cohort studies, with the percentage of successfully removed lesions as primary outcome. Nevertheless, according to most experts, the mainstay of treatment in HS is surgical intervention. Anti-inflammatory agents reduce inflammation, pain, swelling, and purulent discharge, but epithelialized cavities and fistulas will not disappear. When residual lesions are neglected, disease may spread from these sinuses or fistulas into the surrounded healthy cured tissue. To achieve long-term improvement, additional surgical interventions are necessary to remove all remaining lesions that have not responded to medical treatment. Therefore, early referral for additional surgical intervention is recommended to limit the extent of disease. Limited surgery can be performed on an outpatient basis under local anesthesia, and is generally well tolerated.

Unfortunately, there is often a long patient’s and doctor’s delay before surgery is performed, due to lack of knowledge and facilities. The average duration of disease before active surgical intervention is used varies in literature, and not seldom reaches or exceeds a decade. Some dermatologists are not confident enough to perform this specific surgical intervention. Additionally, due to the infiltration depth and the extent of the disease, an accurate surgical procedure can be a time-consuming assignment. In the current Dutch healthcare system, the reimbursement for surgical removal of HS lesions is not sufficient to cover the average costs of the procedure. As a consequence, patients are often referred to academic hospitals for surgery.

**Multifactorial approach**

Based on experience from recent years, it has become common practice in our hospital to treat patients with severe recalcitrant HS with a multifactorial approach. The first step is treatment with two antibiotics (clindamycin 300 mg twice daily + rifampicin 300 mg twice daily) for 2 to 4 months. If patients are not responding to antibiotic treatment, and a clear inflammatory component (purple inflammation around HS lesions, rubor, calor, dolor, fever) is present, a TNF-α inhibitor is added. Subsequently, after an observation period of 3 to 6 months, remaining sinuses and fistulas that do not respond to the anti-inflammatory treatment are removed surgically.
**TNF-α inhibitors**

Today, two TNF-α inhibitors are available for the off-label treatment of patients with recalcitrant HS, infliximab and adalimumab. In our hospital most patients are treated with infliximab intravenously, 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks. Our preference is based on our own experience and the positive results described in several case series and a small RCT. Infliximab was the first drug that was available and for many years also the only drug that was reimbursed. In the recent years, adalimumab has been investigated more extensively in some large high-quality RCTs, which were designed for registration purposes. Adalimumab seems promising when administered in higher doses of 160 mg subcutaneously at week 0, 80 mg at week 2, and then 40 mg weekly. Unfortunately, this higher dosage requirement is accompanied by increasing costs, making adalimumab treatment almost twice as expensive as standard infliximab treatment. Despite the higher costs, an advantage of adalimumab is that after instruction, it can be self-administered as subcutaneous injections. This is different from infliximab, which always needs to be administered in a hospital setting, intravenously. Also, data regarding safety assessment seem to be in favor of adalimumab.

Large additional RCTs to investigate the efficacy and safety of infliximab are not expected, as its patent expired in early 2015. It will be interesting to see how the use of the two biologicals will develop. Adalimumab will probably obtain its registration, and additional reimbursement agreement. Consequently, adalimumab will be regarded as the biological of first choice for patients with severe HS, despite the available, less expensive, and often even more effective infliximab. Government regulations may even forbid further use of infliximab because off-label use of a drug is not allowed in some countries if a registered alternative is available. Meanwhile, several pharmaceutical companies have developed so-called biosimilars. The introduction of these less-expensive biologicals may offer the solution for future reimbursement problems, which would be favorable for the severely affected HS patient.

**Future considerations**

HS has gained more and more attention over the last decade, and we hope this positive tendency will continue. There is a structural need for additional RCTs, not only on biological therapy, but also for the simpler and more widely used conventional medical options. For example an investigator-initiated RCT to examine the role of antibiotics (the combination clindamycin/rifampicin, clindamycin monotherapy, or tetracyclines) versus placebo. Still, the search for the best-suited biological continues, as new options such as ustekinumab and anakinra are being investigated in ongoing trials and results are awaited to be made public.

Besides the medical treatment options, more attention should be paid to integrate surgical treatment of HS patients in daily clinical practice, as surgery is regarded as a crucial step to cure the condition. Around the world more facilities are needed to perform...
surgery. Extensive surgery requires general anesthesia and is usually performed by general surgeons, plastic surgeons or dermatologists. Limited surgery can be performed on an outpatient basis and under local anesthesia, which saves expensive and scarce operating room facilities for more complex procedures. Opportunities have to be created to educate dermatologists so they can perform these surgical interventions themselves. Preferably, this education should be embedded in the standard dermatology residency program, or should be offered in additional training programs for dermatologists. In that way physicians obtain more confidence, and more hospitals will be able to offer this surgery, reducing waiting lists and operational bottlenecks at individual hospitals. The fact that an accurate surgical procedure for HS is generally time-consuming and not lucrative makes it an unpopular procedure to perform. For that reason, health insurance companies should be better informed of the importance of this procedure, its long average duration, and the need for higher financial compensation.

Also health insurance companies should take responsibility and reimburse the off-label use of TNF-α inhibitors and other emerging biologicals for patients with severe HS. In contrast to other indications such as psoriasis, in which case long-term or even life-long treatment is necessary, the use of TNF-α inhibitors in HS may be limited to a shorter period, if treatment is followed by, or combined with, surgical interventions. Using this combined approach, a percentage of the severe HS patients can be cured. We hope that this insight will in time help increase possibilities to treat severely affected HS patients with biologicals. These patients would benefit immensely from effective treatment, as HS is a devastating disease. Its impact on quality of life is even higher than for patients with psoriasis who receive TNF-α inhibitors.
ADDENDUM

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Portfolio
Bibliografie
Dankwoord
Curriculum Vitae
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Randomized controlled trials for the treatment of hidradenitis suppurativa
Authors: D.C. van Rappard, J.R. Mekkes, T. Tzellos

D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

J.R. Mekkes: writing, critical revision and final approval of the version to be published.

T. Tzellos: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

Hidradenitis suppurativa not associated with CARD15/NOD2 mutation: a case series
Authors: D.C. van Rappard, J.R. Mekkes

D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

Four cases of plaque form hidradenitis suppurativa
Authors: D.C. van Rappard, M.V. Starink, A.C. van der Wal, M.A. de Rie, J.R. Mekkes

D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

M.V. Starink: acquisition of data, critical revision and final approval of the version to be published.

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M.A. de Rie: critical revision and final approval of the version to be published.

J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa
Authors: D.C. van Rappard, M.F.E. Leenarts, L. Meijerink-van ’t Oost, J.R. Mekkes

D.C. van Rappard: corresponding author, conception and design, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

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J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review
Authors: D.C. van Rappard, J. Limpens, J.R. Mekkes

D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

J. Limpens: conception and design, acquisition of data, critical revision and final approval of the version to be published.
J.R. Mekkes: conception and design, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

New-onset polyarthritis during successful treatment of hidradenitis suppurativa with infliximab
Authors: D.C. van Rappard, J.E. Mooij, D.L.P. Baeten, J.R. Mekkes
D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.
J.E. Mooij: acquisition of data, critical revision and final approval of the version to be published.
D.L.P. Baeten: analysis and interpretation of data, critical revision and final approval of the version to be published.
J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

Six patients with pyoderma gangrenosum successfully treated with infliximab
Authors: J.E. Mooij, D.C. van Rappard, J.R. Mekkes
J.E. Mooij: acquisition of data, critical revision and final approval of the version to be published.
D.C. van Rappard: corresponding author, conception and design, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.
J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, critical revision and final approval of the version to be published.

Mild to moderate hidradenitis suppurativa treated with local excision and primary closure
Authors: D.C. van Rappard, J.E. Mooij, J.R. Mekkes
D.C. van Rappard: corresponding author, conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.
J.E. Mooij: conception and design, critical revision and final approval of the version to be published.
J.R. Mekkes: conception and design, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.

Treatment of severe hidradenitis suppurativa with infliximab in combination with surgical interventions
Authors: D.C. van Rappard, J.R. Mekkes
D.C. van Rappard: corresponding author, conception and design, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.
J.R. Mekkes: conception and design, acquisition of data, analysis and interpretation of data, writing, critical revision and final approval of the version to be published.
## AMC Graduate School for Medical Sciences PhD Portfolio

**Name PhD student:** Dominique van Rappard  
**PhD period:** December 2010 – October 2015  
**Promotor:** Prof. dr. M.A. de Rie  
**Co-promotor:** Dr. J.R. Mekkes  
**Institution:** Department of Dermatology, Academic Medical Centre, University of Amsterdam

### 1. PhD training

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<th>General courses</th>
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<tr>
<td>• Basic Course Legislation and Organization for Clinical Researchers (BROK)</td>
<td>2011</td>
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<td>• Clinical Data Management</td>
<td>2011</td>
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<td>• Practical Biostatistics</td>
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<td>• Clinical research meeting, every two months</td>
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<td>• Clinical and Scientific Conference, weekly</td>
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<td>• Clinical and Pathological Conference, weekly</td>
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<td>• 41st Annual meeting of the European Society for Dermatological Research (ESDR), Barcelona, Spain. Poster presentation: <em>Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa</em></td>
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<td>• Clinical and Scientific Conference, Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands. <em>Surgery for hidradenitis suppurativa</em></td>
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<td>• Clinical and Scientific Conference, Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands. <em>Etiology of hidradenitis suppurativa</em></td>
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<td>• 19th Congress of the European Academy of Dermatology and Venereology (EADV), Gothenburg, Sweden</td>
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<td>• 41st Annual meeting of the European Society for Dermatological Research (ESDR), Barcelona, Spain</td>
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<td>• 23th Congress of the European Academy of Dermatology and Venereology (EADV), Amsterdam, The Netherlands</td>
<td>2014</td>
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<td>• Hugh Greenway’s superficial anatomy and cutaneous surgery, San Diego, USA</td>
<td>2015</td>
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<td>• Dermatology Immunology foundation Symposium ‘Acne and Rosacea of the year 2010’, Amsterdam</td>
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<td>• Jubileum congress ‘Vascular Birthmarks’, HEVAS, Amsterdam</td>
<td>2010</td>
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1. Oral pathology, Amsterdam 2014 8
• Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV) 2012, 2013, 2014 60
• Dermatoloog in opleiding (DIO) dagen, Amersfoort 2013, 2014, 2015 30
• Jaarsymposia Dermatologie en Wetenschappelijke vergaderingen NVDV 2011-2015 80

2. Teaching

Supervising

• Supervision master student, University of Amsterdam, master thesis: Efficacy of pulse dye laser treatment in patients with rosacea. 2012 20

3. Publications

In this thesis


• van Rappard DC, Starink MV, van der Wal AC, de Rie MA, Mekkes JR. Four cases of plaque form hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2015, in press.


Other


Occasional reviewer for the following journals

• International Journal of Dermatology

• Journal of Investigative Dermatology

• Journal of the European Academy of Dermatology and Venereology


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Lieve Olivier, mijn liefste kleine broertje, omdat je de grote afwezige bent op 13 oktober en tijdens de rest van mijn verdere leven, zal je op deze pagina niet ontbreken. Ik hou van je.
CURRICULUM VITAE
