

Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review

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Summary

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Hidradenitis suppurativa (HS) is a difficult disease to treat. Although the pathogenesis of this inflammatory skin disease is largely unknown, the important role of the immune system has been demonstrated in both experimental and clinical studies. Clinicians are therefore increasingly prescribing systemic treatments with immunosuppressive agents, but the more traditionally used systemic retinoids, especially isotretinoin, also remain relatively common therapies. In order to provide an overview of all currently available systemic immunosuppressive agents and retinoids for the treatment of HS, a systematic search was performed using the Medline and Embase databases. All published papers concerning systemic retinoids or immunosuppressive treatments for HS in adults were included. The primary endpoints were the percentages of significant responders, moderate responders and nonresponders. Other endpoints were the relapse rate and adverse events. In total 87 papers were included, comprising 518 patients with HS who were treated with systemic retinoids, biological agents or another immunosuppressive agents, including colchicine, ciclosporin, dapsone or methotrexate. The highest response rates were observed with infliximab, adalimumab and acitretin. Overall, the quality of evidence was low and differed between the agents, making direct comparisons difficult. However, based on the amount of evidence, infliximab and adalimumab were the most effective agents. Acitretin was also effective in HS, although the quality of the evidence was low. The therapeutic effect of isotretinoin is questionable. Randomized controlled trials are needed to confirm the effectiveness of acitretin, and to identify the most effective immunosuppressive agents in HS.

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic inflammatory skin disease characterized by recurrent, painful, deep-seated nodules and abscesses. In an advanced stadium, sinus tracts are formed, eventually leading to fibrotic scars, dermal contractures and induration of the skin.^{1,2} Lesions typically occur on inverse, apocrine-gland-bearing skin, like the axillary, inguinal and anogenital regions. Quality of life is greatly impaired in HS.^{3,4} In addition to lifestyle changes, therapeutic options include topical and systemic antibiotics, antiandrogens, systemic retinoids, immunosuppressive agents, laser treatment and surgery.⁵⁻⁷ As an effective monotherapy is lacking, combination of different treatment modalities is often required to achieve some improvement.

Although the pathogenesis of HS is largely unknown, follicular hyperkeratinization followed by follicular occlusion is a primary feature of HS.⁸⁻¹¹ Several factors probably contribute to these histological changes, including smoking,

sweating, obesity and hormonal changes.¹² The important role of the immune system in HS has been underlined in recent studies, where several associations have been observed, including involvement of the interleukin (IL)-12/Th1 and IL-23/Th17 pathways, and increased tumour necrosis factor α in the skin and serum.¹³⁻¹⁵ In addition, there is a deficiency of IL-22 and IL-20 in lesional HS skin, leading to decreased antimicrobial protein levels, making the skin prone to bacterial infection.¹⁶

In conclusion, both clinical and experimental studies support the use of anti-inflammatory drugs and retinoids in the treatment of HS, and several different types of these agents are currently available. However, there is no consensus on which agent is most effective for the treatment of HS. Therefore, this review aims (i) to evaluate all existing evidence to date for the use of systemic immunosuppressive agents and systemic retinoids in HS, and (ii) to assess their current position in the treatment of HS.

Patients and methods

Inclusion and exclusion criteria

Included in the study were all fully published papers that reported on the clinical effects of any systemic immunosuppressive agents or systemic retinoids in HS localized at the typical inverse regions. Patients had to be aged 18 years or older. Studies not exclusively dealing with HS were excluded, unless data for HS could be extracted separately. Studies were excluded if insufficient details were given on the treatment regimen in respect of dosing, treatment duration and concomitant immunosuppressive medication. There were no language restrictions.

Types of outcome measures

The efficacy of treatment was classified for each patient as 'significant response', 'moderate response' or 'nonresponse'. A significant response was defined as a reduction of the Sartorius score of $\geq 50\%$, improvement in quality of life of $> 50\%$, or if stated so by the authors. A moderate response comprised score reductions $< 50\%$, or if stated so by the authors. The primary endpoints comprised the percentages of significant responders, moderate responders and nonresponders. If a study did not report individual results, all patients from that study were categorized corresponding to the reported mean results. Dropouts were considered to be nonresponders. The secondary endpoint was the percentage of responders who relapsed during or after discontinuation of treatment, and the tertiary endpoint comprised adverse events (AEs).

Identification of studies

Databases were systematically searched by two independent authors (S.vH. and J.L.B.) for studies dated up to May 2012. A search was conducted using Embase [search terms: 'hidradenitis suppurativa'/exp OR 'hidradenitis suppurativa' OR (hidraden* AND suppurativ*) OR 'acne inversa' OR 'inverse acne'] and Medline [search terms: 'hidradenitis suppurativa'(MeSH) OR (hidraden* AND suppurativ*) OR 'acne inversa' OR 'inverse acne']. Reference lists of included papers and relevant reviews were manually searched to identify additional papers.

Data extraction and analysis

Two authors (J.L.B. and S.vH.) independently conducted data extraction using standardized forms. Discrepancies between the researchers were resolved through discussion. Authors were not contacted for missing data.

Data were analysed by means of descriptive statistics.

Quality assessment

The quality of evidence was assessed by grading as follows: A, systematic review or meta-analysis, randomized controlled trial

with consistent findings, or all-or-none observational study; B, lower-quality clinical trial or study with limitations and inconsistent findings, cohort study or case-control study; or C, consensus guidelines, usual practice, expert opinion or case series.¹⁷

Results

Figure 1 shows the process of study selection, at the end of which 87 papers were included, comprising a total of 518 patients. The immunosuppressive therapies evaluated in these papers were biologics, colchicine, ciclosporin, methotrexate and dapson. Treatment with systemic retinoids included the use of acitretin and isotretinoin. Two papers dealt with two immunosuppressive agents and these studies are therefore discussed in subheadings of the Results section.^{18,19} The level of evidence of the included papers is described in Table 1 for each immunosuppressive agent. A summary of the results is described in Figure 2.

Biologics

Adalimumab

Studies We identified 15 papers studying a total of 68 patients.^{18–32} One study had a randomized, double-blind, placebo-controlled design (evidence level A).³¹ In one retrospective cohort study, the effectiveness of adalimumab was compared with infliximab (evidence level B).¹⁹ Four other studies had an evidence level of B,^{20,21,23,32} and the remaining nine studies were level C.^{18,22,24–30} Dosing regimens varied from 40 mg to 80 mg, in a frequency ranging from weekly to every other week. The treatment duration was ≥ 1 year in three studies,^{21,24,26} ≤ 6 months in six studies^{18,20,22,27,31,32} and unclear in six studies.^{19,23,25,28–30} One patient was simultaneously treated with adalimumab and methotrexate for the first 2 months.²⁶ The follow-up time varied between studies, ranging from 13 weeks to 29 months.

Primary endpoints In total, 30/68 patients (44%) showed a significant response to adalimumab, 24 patients (35%) had a moderate response and 14 patients did not respond (21%) (Fig. 2).

Secondary endpoints One paper reported that the majority of the seven responding patients showed recurrence of HS after 1 year of follow-up; however, individual numbers could not be extracted.¹⁹ Occurrence of relapse was described for 35 of the remaining 42 responders: 23/35 (66%) relapsed within 3–10 months after discontinuation of treatment.^{21,23,25,26,28,31} Seven of the 35 responders (20%) relapsed during treatment, but symptoms improved in all of them when the dose of adalimumab was increased.^{23,26,28}

Tertiary endpoints Adverse events are described in Table 2. Six papers did not report on AEs.^{22,24,27,29,30,32}

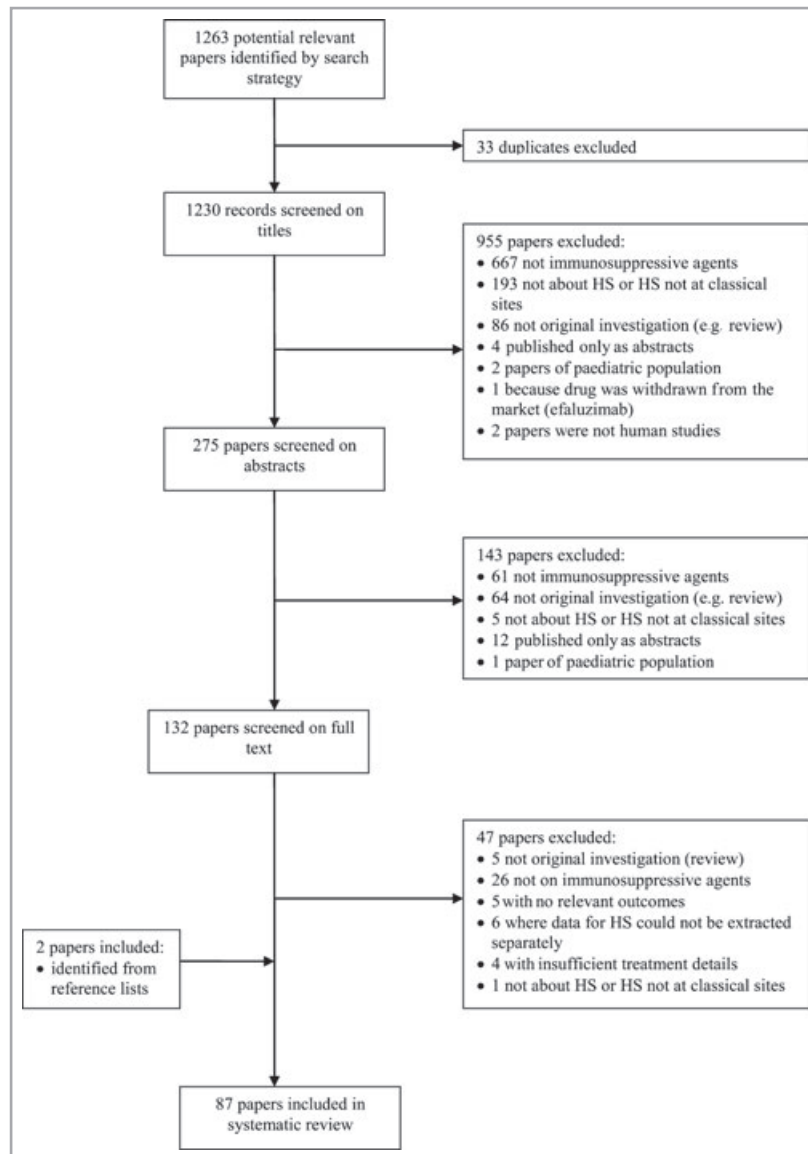


Fig 1. Study selection.

Etanercept

Studies Nine papers comprising 54 patients evaluated the effect of etanercept on HS.^{18,33–40} One study had a randomized, double-blind, placebo-controlled design (evidence level A); however, after 12 weeks all patients received open-label etanercept.³³ We included only those 10 patients who were initially allocated to the etanercept group. Five papers had evidence level B^{34,35,37,39,40} and three papers level C.^{18,36,38} Dosing schedules varied from 25 mg to 50 mg once or twice weekly to 100 mg weekly. Treatment duration was 3 months in two papers,^{34,35} 6 months in two^{33,39} and around 1 year or longer in four papers.^{18,36–38} The follow-up time was 17–144 weeks. Long-term results of the patients described by

Giamarellos-Bourboulis *et al.*³⁵ were reported in a separate paper.⁴¹

Primary endpoints A significant response to etanercept was observed in 21/54 patients (39%), whereas nine patients (17%) had moderate improvement and 24 patients (44%) did not respond to the treatment (Fig. 2).

Secondary endpoints In total 18/30 responders (60%) relapsed after treatment was discontinued. The time to relapse ranged from immediately after stopping of treatment to 8 months thereafter, but the majority had recurrence of HS lesions within 2 months.

Tertiary endpoints Table 2 describes the tertiary endpoints. One study did not report on AEs.¹⁸

Table 1 Level of evidence for all included studies

Immunosuppressive agent (total number of papers)	No. of level A evidence (% of total within group)	No. of level B evidence (% of total within group)	No. of level C evidence (% of total within group)	Percentage of responders	Percentage of nonresponders
Biologics (66)	3 (5)	17 ^a (24)	48 ^b (71)		
Adalimumab (15)	1 (7)	5 (33)	9 (60)	79	21
Etanercept (9)	1 (11)	5 (56)	3 (33)	56	44
Infliximab (42)	1 (2)	7 (17)	34 (81)	89	11
Ustekinumab (2)			2 (100)	75	25
Retinoids (13)		6 (46)	7 (54)		
Acitretin/etretinate (6)		2 (33)	4 (67)	95	5
Isotretinoin (7)		4 (57)	3 (43)	36	64
Other (8)		2 (25)	6 (75)		
Ciclosporin (3)			3 (100)	100	0
Dapsone (3)			3 (100)	56	44
Colchicine (1)		1 (100)		25	75
Methotrexate (1)		1 (100)		0	100

^aOne paper compared adalimumab with infliximab, and is included as level B for both adalimumab and infliximab.¹⁹ ^bOne paper describes the efficacy of adalimumab and etanercept; therefore it has been included as level C for both adalimumab and etanercept.¹⁸

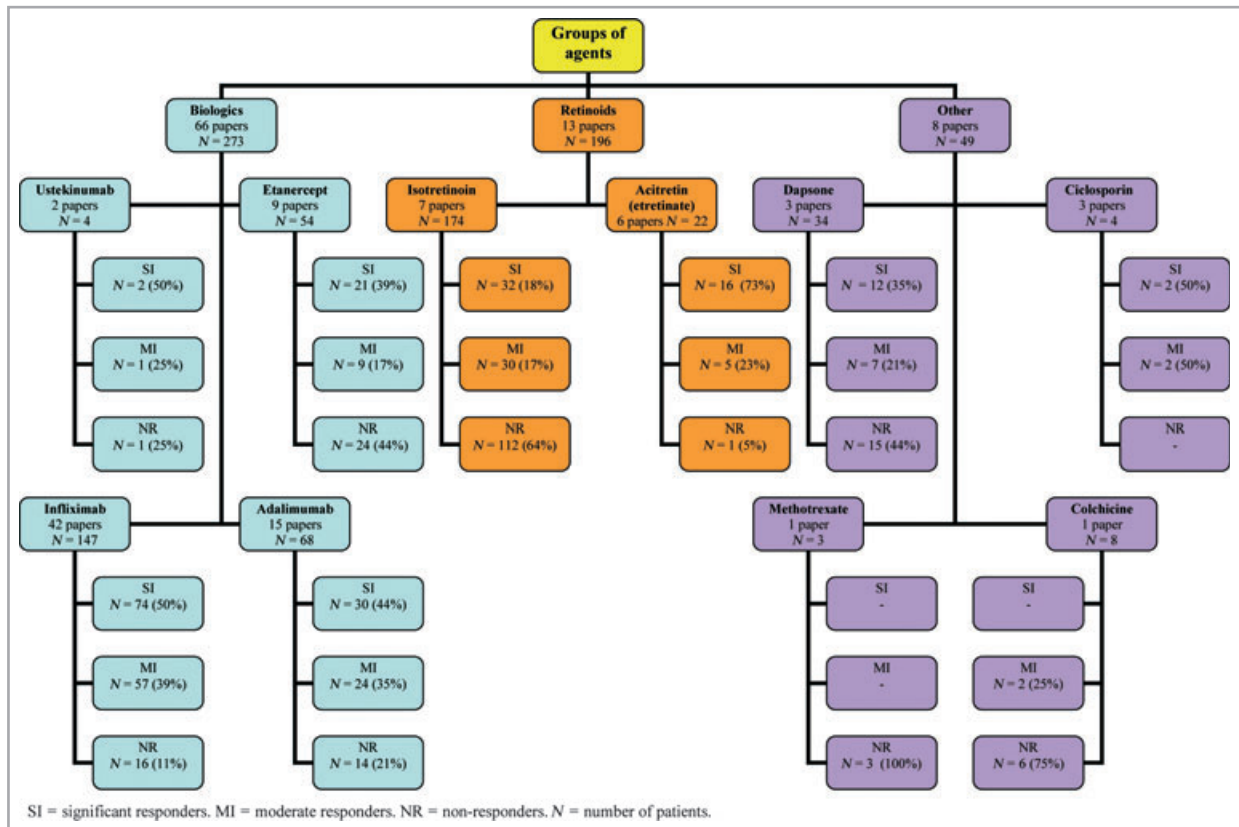


Fig 2. Overview of total number of papers and treated patients for each agent, including response rates. SI, significant response; MI, moderate response; NR, nonresponders; N, number of patients.

Infliximab

Studies The efficacy of infliximab was evaluated in 42 papers, comprising 147 patients. One study had a randomized, double-

blind, placebo-controlled design (evidence level A), but after 8 weeks all patients received infliximab.⁴² Only those 15 patients who were initially allocated to infliximab were included. Evidence levels B and C were found in seven^{19,43-48} and 34 studies,⁴⁹⁻⁸² respectively. One study compared the effect

Table 2 Adverse events (AEs) observed in the studies

Immunosuppressive agent (number of patients treated)	Observed AEs (frequency)	Number of patients who discontinued treatment due to AEs
Adalimumab (68)	Painful injection site, ^a mild infections (10), nonspecific gastrointestinal symptoms (3), nonspecific rash (3), fatigue (3), elevated liver enzymes (2), severe infusion reaction with urticaria (1), reactivation of Epstein–Barr virus (1), facial cellulitis (1), irritation of ears (1), hoarseness (1), headache (1), dry eyes (1), muscle chest pain (1), dry skin (1), hay fever (1)	1 ²³
Etanercept (54)	Injection site reactions, ^a upper respiratory tract infection (4), nausea (3), paraesthesias (2), chest pain (2), cellulitis (2), elevated cholesterol (1), muscle cramps (1), flu-like symptoms (1), hypertension (1)	3 ³⁴
Infliximab (147)	Nonspecified side effects (14), acute arthritis/myalgia (8), headache (7), hypersensitivity reactions (5), influenza-like illness (4), numbness in legs/neuropathy (3), skin rash (3), dizziness (3), asthenia (3), anaphylactic shock (1), pneumococcal sepsis (1), localized tuberculosis infection (1), pustular lesions on lower limbs (1), fever (1), hypertension (1), colon cancer (1), herpes zoster (1), cervical abscess (1), dyspnoea (1), lupus-like reaction (1)	31 ^{43–46,48,57,63,68,72,73,75,76,78–80}
Ustekinumab (4)	Cystitis (1), psoriasiform dermatitis (1), hidradenitis suppurativa lesions infected by <i>Staphylococcus aureus</i> (1)	None
Isotretinoin (174)	Cheilitis/xerosis (15), 'usual side effects' ^b (3), arthralgia (1), headache (1)	10 ⁸⁶
Acitretin/ etretinate (22)	Cheilitis/xerosis (13), alterations in lipids (4), altered triglyceride levels (3), sticky skin/hypertrichosis/photosensitivity (2), alopecia (2), elevated cholesterol (2), headache (1), loss of concentration (1), joint pain (1), buzzing in ears (1), depression/fatigue (1)	2 ^{92,95}
Dapsone (34)	Anaemia/haemolysis (4), nausea (3), dizziness (2), tiredness (2), headache (2), elevated bilirubin (1), rash (1), gloomy mood (1), malaise (1)	None
Colchicine (8)	Nausea (3), diarrhoea (3)	1 ¹⁰¹
Methotrexate (3), ciclosporin (4)	Adverse events not stated	None

^aSome studies reported that this event occurred in 'several patients', without mentioning exact numbers. ^bProbably xerosis/cheilitis.

of infliximab with another treatment, namely adalimumab.¹⁹ Almost all of the 147 patients received intravenous infliximab 5 mg kg⁻¹ at weeks 0, 2 and 6. In 10 studies treatment was discontinued after these three administrations.^{19,46,57,61,63,65–67,70,82} However, the majority of patients received maintenance therapy every 6–8 weeks. Dosing schedules were not clear in five papers.^{50,69,71,74,75} The duration of treatment was > 1 year in nine studies.^{45,48,49,53,56,60,64,79,80} In four papers, in addition to infliximab, patients received methotrexate, which might have prevented the formation of autoantibodies.^{45,49,60,64} Simultaneously to infliximab, patients were treated with azathioprine in two studies,^{70,72} prednisolone in one study,⁷⁷ prednisolone and ciclosporin in one study⁶⁸ and with oral azathioprine and methylprednisolone in one study.⁷¹

Primary endpoints A significant improvement was seen in 74/147 patients (50%); 57 patients (39%) showed moderate improvement and 16 patients (11%) had no response (Fig. 2).

Secondary endpoints Only 10/131 responders (8%) experienced recurrence of HS during treatment,^{48,49,55,60,68,79} and 26 responders (20%) relapsed within 2 weeks to 3 years after discontinuation of therapy.^{42,46,52–54,57,62,63,67,73,75} One paper reported that the majority of patients had recurrence of HS

1 year after discontinuation of treatment; however, individual numbers could not be extracted.¹⁹

Tertiary endpoints Fourteen studies did not report on AEs.^{50,52,55,59–61,65,66,69–71,74,78,82} AEs were observed in 19 studies (Table 2).^{19,42–48,57,63,64,68,72,73,75,76,79–81}

Ustekinumab

Studies Two papers comprising a total of four patients evaluated the effect of ustekinumab (both evidence level C).^{83,84} The patients received 45 mg ustekinumab at weeks 0, 4 and 12. Subsequently, one patient received injections every 3 months,⁸⁴ and three patients every 2 months.⁸³ Three patients were treated for at least 6 months, two of whom were probably still on treatment at the time the paper was written.⁸³

Primary endpoints Two of the four patients (50%) showed a significant response, one patient had a moderate response (25%) and one patient (25%) did not respond (Fig. 2).

Secondary endpoints One responding patient had temporary relapses every 2 weeks prior to his next injection, but

improved after administration.⁸⁴ In another responding patient, lesions recurred after 6 months;⁸³ the dose of ustekinumab was therefore increased to 90 mg and his disease has improved ever since. The remaining one responding patient did not relapse during treatment.⁸³

Tertiary endpoints Adverse events were reported in one paper (Table 2).⁸³

Retinoids

Isotretinoin

Studies Seven papers evaluated the effect of oral isotretinoin, and comprised a total of 174 patients. Level B evidence was found in four papers^{85–88} and level C in three.^{89–91} The daily dosages of isotretinoin were 0.5–1.2 mg kg⁻¹ and treatment duration was 4–12 months. One patient was pretreated with prednisone and erythromycin, followed by the gradual introduction of isotretinoin.⁸⁹

Primary endpoints Significant improvement was observed in 32/174 patients (18%), moderate improvement in 30/174 patients (17%) and no response was observed in 112 patients (64%) (Fig. 2).

Secondary endpoints One study comprising 14 responders did not mention whether recurrences occurred after cessation of therapy.⁸⁵ Of the remaining 48 responders, six patients (12%) relapsed within a couple of months after discontinuation of treatment.

Tertiary endpoints Two studies did not report on AEs.^{85,89} All of the remaining 18 patients experienced AEs (Table 2).

Acitretin and etretinate

Studies Acitretin is a metabolite of etretinate and has replaced treatment with etretinate in a variety of disorders, as it has a much shorter elimination half-life and is equally effective. Six papers reported on the treatment of HS with these retinoids, and comprised 22 patients.^{92–97} The level of evidence was B in two studies;^{92,96} the remaining papers were level C. Patients treated with etretinate received daily doses of 0.35–1.1 mg kg⁻¹, and the daily doses for acitretin ranged from 0.25 mg kg⁻¹ to 0.88 mg kg⁻¹. The duration of treatment was 3–39 months.

Primary endpoints Significant improvement was seen in 16 of 22 patients (73%), five patients (23%) improved moderately and one patient (5%) did not respond to the therapy (Fig. 2).

Secondary endpoints No relapses during therapy were described. Acitretin or etretinate treatment was eventually discontinued

in 17 patients. Within 6 months after cessation of therapy, six of the 17 patients (35%) had recurrence. Eight patients (47%) relapsed > 1 year after discontinuation of treatment.

Tertiary endpoints The AEs that were reported are shown in Table 2. Two studies did not report on AEs.^{93,97} For one study, data on AEs could not be extracted separately for HS.⁹⁶

Other therapies

Dapsone

Studies The effect of dapsone was described in three papers, all with evidence level C.^{98–100} In total 34 patients were treated with doses of 25–200 mg daily during 0.5–48 months. The majority of patients were still on treatment at the time of study closure.

Primary endpoints A significant improvement was seen in 12/34 patients (35%), seven patients (21%) had a moderate response and 15 patients (44%) did not respond (Fig. 2).

Secondary endpoints Two studies reported that discontinuation of therapy led to a rapid recurrence of HS lesions in all patients, and that dapsone treatment could therefore not be terminated.^{99,100} Two out of nine responders in the study of Yazdanyar *et al.*⁹⁸ also rapidly relapsed after cessation of treatment; however, reintroduction of dapsone led to rapid improvement.

Tertiary endpoints Adverse events are shown in Table 2.

Colchicine

Studies We identified one paper (evidence level B) describing eight patients who were treated with colchicine 0.5 mg twice daily during 4 months.¹⁰¹

Primary endpoints Two out of eight patients (25%) had a moderate response and six out of eight patients (75%) did not respond to colchicine (Fig. 2).

Secondary endpoints These were not stated.

Tertiary endpoints The observed AEs are shown in Table 2.

Ciclosporin

Studies We identified three papers (evidence level C) on ciclosporin.^{102–104} Four patients were treated with ciclosporin 2–6 mg kg⁻¹ daily for 4–15 months. Two patients were concomitantly treated with prednisolone or oral antibiotics.^{102,103}

Primary endpoints A significant response was observed in two of the four patients (50%) and the remaining two patients had a moderate response (Fig. 2).

Secondary endpoints In one patient ciclosporin was discontinued after 4 months, leading to a recurrence 4 months later.¹⁰² Two patients were still on treatment at the time the paper was published and did not experience any relapses. It was not reported whether the last patient experienced a relapse.¹⁰⁴

Tertiary endpoints These were not reported in any of the studies.

Methotrexate

Studies We identified one paper that reported on the effectiveness of methotrexate in HS.¹⁰⁵ It concerned an open study in which two patients received a weekly dose of 12.5 mg and one patient received 15 mg. Treatment duration was 6 weeks, 4 months or 6 months.

Primary endpoints None of the three patients responded to treatment with methotrexate (Fig. 2).

Secondary endpoints As none of the patients showed a response to the treatment, time to relapse was not applicable.

Tertiary endpoints Adverse events were not reported.

Discussion

To the best of our knowledge, this is the first systematic review specifically aimed at analysing all currently available evidence of immunosuppressive agents and systemic retinoids for the treatment of HS. In total 518 patients were analysed, divided over 87 papers. The majority of patients ($n = 273$) were treated with a biological agent. Overall, the quality of the included papers was low; only three randomized controlled trials were identified, all on biologics.^{31,33,42} The majority of papers were case reports or series, bringing along a risk of publication bias. Two papers were not identified by our search strategy due to the fact that they were not incorporated in Medline or Embase.^{96,97}

Based on our results, the most effective agents for HS were infliximab, adalimumab and acitretin, with 89%, 79% and 95% of patients, respectively, responding to treatment. However, as the results for acitretin were based on far fewer patients and were of a lower level of evidence than the results for infliximab and adalimumab, caution must be taken when directly comparing the efficacy of these agents. The positive results of infliximab and adalimumab are in accordance with the findings of van Rappard *et al.*¹⁰⁶ Acitretin for HS is barely mentioned in the literature; however, its positive effect is pharmacologically reasonable, as the primary event in HS is follicular occlusion, and acitretin induces normalization of epithelial cell proliferation and differentiation.^{107,108} Not

surprisingly, isotretinoin is ineffective for HS, as this agent primarily works on sebaceous glands, which are not involved in the pathogenesis of HS.^{109,110} The observation that 35% of treated patients still responded to isotretinoin is more likely to be due to the immunomodulatory effects of this retinoid.¹¹¹

The highest quality of evidence was identified for etanercept, which enables us to conclude that the efficacy (56% responders) was relatively low. Only a few patients have been treated with ustekinumab, ciclosporin, dapsone, methotrexate and colchicine. It has been shown that the IL-12/IL-23 pathway is upregulated in HS, therefore there is a rationale for the efficacy of ustekinumab (an inhibitor of this pathway), and the first results of this agent are indeed promising.^{83,84} However, clinical trials are needed to confirm its effect. The same applies for ciclosporin; although all patients responded to treatment, this agent has been studied in only four patients, making it impossible to draw any definite conclusions. The efficacy of dapsone is doubtful, methotrexate as a monotherapy seems of little value and colchicine is not effective in HS.

Although long-term results and relapse rates were not available for many papers on biologics, recurrence of HS occurred frequently during therapy or within a couple of months after cessation of biological therapy. In contrast, Boer and Nazary⁹² achieved long-term remission (i.e. > 1 year) in a majority of patients treated with acitretin, indicating that this is probably also effective in the long term. However, this observation needs to be confirmed in larger trials as only 12 patients were included.

Adverse events were observed with all agents, except for ciclosporin and methotrexate, where it was not stated. The highest number of withdrawals due to AEs occurred with infliximab and isotretinoin. Other reviews also showed that the risk of withdrawal is higher during infliximab therapy compared with adalimumab and etanercept.^{106,112} The most common AE during acitretin therapy was cheilitis, which can be very disturbing for patients. Moreover, the most important disadvantage of acitretin is that it has extremely teratogenic side-effects.¹¹³ Therefore, this agent should be mainly reserved for men and sterilized or postmenopausal women.

A limitation of this review, and any other review on HS treatment, is heterogeneity between the studies in respect of study design, the number of included participants, the severity of HS and the timing and methods for outcome assessments. Therefore, caution must be taken in directly comparing the different treatment options for HS.

In conclusion, this review indicates that, based on the evidence today, infliximab and adalimumab are the most effective immunosuppressive agents for HS. Additionally, acitretin is a promising agent and definitely worth considering in men and sterilized or postmenopausal women, although high-quality evidence is lacking for its administration in HS. Also, these data strongly indicate that there is a need for randomized controlled clinical trials in order to identify the most effective treatment targets and the most effective therapy for HS.

What's already known about this topic?

- The immune system is important in the pathogenesis of hidradenitis suppurativa (HS).
- Treatment of HS is difficult and usually comprises antibiotics, antiandrogens, laser treatment or surgery.
- Systemic immunosuppressive and retinoid therapies are frequently prescribed; however, little is known about which agents are most effective.

What does this study add?

- Infliximab, adalimumab and acitretin are the most effective systemic agents, although the quality of evidence for acitretin is lower than that for infliximab and adalimumab.

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