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REVIEW

Therapies for hidradenitis suppurativa: a systematic review with a focus on Brazil

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Abstract

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease associated with a significant negative impact on the quality of life of patients.

Methods: We conducted a systematic review to assess current treatment for HS, with a special focus on therapies approved or used in Brazil. We used the PICO framework to improve the research process. The systematic review was reported in line with the PRISMA statement checklist. The search was conducted with clinical questions on two global databases (PubMed (MEDLINE) and Google Scholar) and three databases especially selected to retrieve Brazilian outcomes (BVS, SCIELO and REDALYC).

Results: Overall, 4640 articles were screened, 182 articles were analysed and 70 were used in a thematic qualitative analysis. Of these, 12 articles were from Brazil. The evidence-based literature was largely limited to case reports, case series, observational studies and expert opinion. Topical therapy, lifestyle interventions and oral antibiotics appeared as effective measures for mild HS. However, moderate-to-severe HS remains refractory to conventional treatments.

Conclusion: Some biologic agents, such as adalimumab, infliximab, ustekinumab and secukinumab, have been shown to be effective in the management of moderate-to-severe HS that failed conventional treatment and demonstrated a good tolerability and safety profile.

Keywords: biologic agents, chronic inflammatory skin disease, hidradenitis suppurativa, secukinumab.

Citation

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Introduction

Hidradenitis suppurativa (HS), or acne inversa, is a chronic inflammatory skin disease characterized by painful, recurrent inflammatory nodules and abscesses that tend to rupture and lead to the formation of sinus tracts and scarring.[1–9] Typically, HS involves the intertriginous areas, mostly the localizations of the body rich in terminal hair follicles and apocrine glands such as the axillary, inguinal, anogenital and gluteal regions.[1–7] Recently, HS was categorized as a subtype of autoinflammatory keratinization disease.[2,3]

The prevalence of HS is reported to vary from 0.03% to 4.0% but it has been suggested that the real prevalence may be around 1%.[4–7] Symptoms predominantly manifest in adults, starting during or after adolescence. Early onset is associated with a positive family history of HS and more widespread disease.[6–9]

Besides a genetic predisposition, HS has been closely linked to different comorbidities. Obesity, female sex and smoking are the most commonly associated epidemiological factors. Smoking and obesity also appear to play a role as predisposing factors. Other comorbidities reported in patients with HS patients are diabetes mellitus, hypertension, thyroid disorders, polycystic ovarian syndrome, inflammatory bowel disease, arthritis, spondylitis, synovitis and pustulosis. Psychiatric coexisting disorders, such as anxiety, depression and smoking habits, have been also frequently reported.[2–8]

HS has a deep and long-standing adverse impact on patient quality of life, often leading to social withdrawal, low self-esteem, unemployment and depression. It is commonly reported that patients are only diagnosed after long delays, ranging from 7 to more than 10 years, increasing patient suffering.[2,7–9]

Additionally to its manifestation as a single disease, HS can also be the main expression or a secondary feature of certain autoinflammatory syndromes. Therefore, syndromic HS has been included in the group of autoinflammatory diseases.[8,10–13]

Management of HS includes a combination of medical and surgical modalities along with additional measures to address comorbidities and complications. Topical treatments, oral antibiotics and lifestyle modifications may be suitable for mild HS.[1,14–17] However, many cases of HS tend to progress in severity and remain resistant to conventional treatments. Recent advances in the knowledge of the key inflammatory mediators support the role of biologic and other immunomodulatory agents for the targeted treatment of moderate-to-severe HS.[14–18] Currently, many therapeutic alternatives are available, and the best options for clinical management are chosen on an individual basis.[1,9,17] Therefore, we conducted a systematic review to assess current medical therapies for HS with a special focus on Brazil.

Methods

Procedures

A search of the literature was performed; the main question was 'What therapies are used for the treatment of hidradenitis suppurativa?'. Alternative or auxiliary literature searches were conducted combining global results with those from Brazil. To improve the research process, we used the PICO framework (Patients–Intervention–Comparison–Outcomes).[19] PICO is a framework that addresses themes by developing clinical research questions prior to starting the research. According to the PICO system, the main search frame was as follows:

P. Patients/Population/Problem: HS

I. Intervention: Available medical treatments

C. Comparison: Treatments approved/used in Brazil

O. Outcomes: Review on effectiveness and safety

The systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.[20]

Research questions

The main PICO question evaluated medical therapies for HS worldwide. As the treatment of HS has been through major changes in recent years due to the adoption of biologic agents, the search was limited to recent years in order to obtain updated information. Medical therapies were the focus of the review; hence, non-conventional treatments and surgical approaches were excluded from the search. Auxiliary PICO questions assessed the epidemiology and demographics of HS and the effectiveness and safety of treatments.

Databases

Public and open access databases were selected for this bibliographic search. Latin American databases were included to also retrieve Brazilian papers, using 'Brazil' as term or 'Portuguese' as language limit. The query that retrieved the greater number of items was selected for each database. The searched databases were PubMed (MEDLINE); Google Scholar; Biblioteca Virtual en Salud (BVS); Scientific Electronic Library Online (SCIELO); and Red de Revistas Científicas de América Latina y el Caribe (REDALYC).

Search process

Initially, a highly sensitive search was performed in order to retrieve as many relevant references as possible from each database. The framework query strategy was conducted with various combinations of key themes (treatment, epidemiology, demographics, effectiveness, safety, Brazil), MESH terms and free text. Boolean operators have also been used to expand or narrow the search as needed for greater precision of the results. Filters and limits were applied in order to retrieve the most recent and relevant results. All databases were searched up to August 20, 2020. Articles electronically published ahead of print were also included.

Results

Five databases were searched, including two global databases (PubMed and Google Scholar) and three Latin American databases (BVS, SCIELO and REDALYC). Overall, 4640 articles were retrieved, 194 articles were screened and 70 were used in the qualitative analysis.[1–18,21–66] Of these, 12 articles were from Brazil.[1,56–66]

In PubMed (MEDLINE), a total of 2834 items were retrieved through a query for HS in all fields. Progressive application of terms, filters and limits yielded 162 items, and a manual selection based on key words such as "Brazil", demographics and epidemiology yielded 70 non-duplicated citations as the final result (Figure 1). The PubMed results final list was compared to the subsequent searches to find new and relevant articles.

A similar process was performed in Google Scholar. From a total of 2530 citations in the initial query ("Hidradenitis suppurativa" in "title"), after applying different terms, fields and limits, 198 items were retrieved. Results after manual selection yielded 53 items, which were compared with those retrieved through PubMed after, cleaning duplicated items. No new articles were retrieved in comparison with the PubMed results.

A total of 2880 records were retrieved in the BVS first query ("Hidradenitis suppurativa" in "title, abstract") and the application of fields, limits and subjects reduced the yielding to 30 records. The BVS search retrieved many duplicated citations as it is made up of different databases. Manual selection, including cleaning of duplicated items, yielded 18 items as a final result. Figure 2 shows the BVS search flow diagram. The SCIELO and REDALYC searches added one article each to the BVS results.

Figure 1. Flow diagram of search strategy and results in PubMed (MEDLINE).

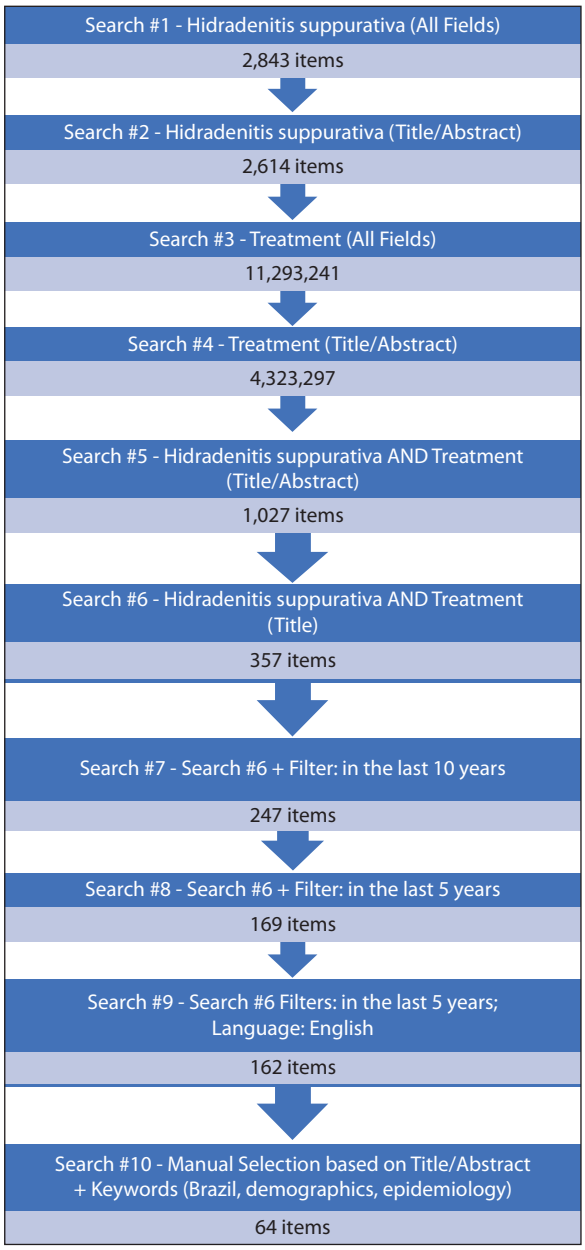


Figure 2. Flow diagram of search strategy and results in BVS (Biblioteca Virtual en Salud).

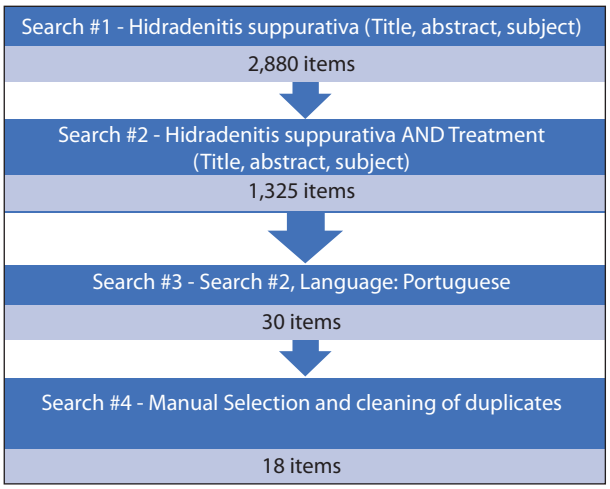
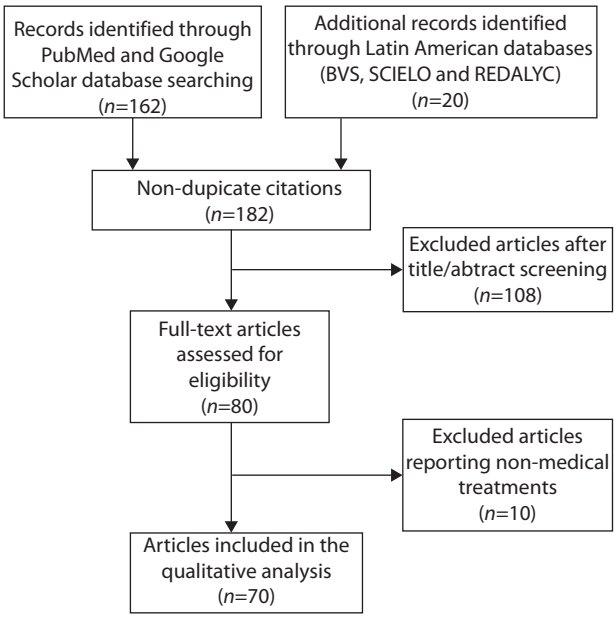


Figure 3. Flowchart showing integrated results from five databases according to PRISMA methodological approach for systematic reviews.



A flowchart in line with PRISMA methodology shows integrated results (70 articles) retrieved from the five databases (Figure 3). These 70 articles were used to obtain the mainstay data for the framework qualitative analysis of current HS treatment.

Staging approach to treatment

Therapeutic strategies have rapidly progressed in the last decade and include the use of topical therapies, systemic antibiotics and a wide range of immunomodulating medications. Localization, scarring, severity, impact and progression are objective drivers of therapeutic choices.

The Hurley staging system of HS is a clinical intuitive classification useful for surgical planning.[7,9,25,28,29,37,44,49,57,60,63]

Scoring systems, such as (Hidradenitis Suppurativa Clinical Response (HiSCR),[1,5,37,38,51] and HS Physician's Global Assessment (HS-PGA),[9,23,50] have been developed to determine efficacy of interventions. The modified Sartorius Score[50,51] and International Hidradenitis Suppurativa Severity Score System (IHS4)[1,41] are both used as severity indexes and outcome measures.

The HiSCR score is an HS-specific scoring system for patients with three or more abscesses or inflammatory nodules. Response to a drug agent is considered when a 50% reduction in nodule and abscess count is achieved without an increase

in fistulas. Partial response corresponds to a 25% reduction in this count. Some authors use HiSCR75, which indicates a high response, measuring at least a 75% reduction from baseline in the total count of abscesses and inflammatory nodules.[1,5,37,38]

IHS4 is a validated tool to dynamically assess HS severity. The IHS4 score is arrived at by the sum of the number of nodules plus the number of abscesses (multiplied by 2) plus the number of fistulas (multiplied by 4). A total score of ≤3 points indicates mild disease, 4–10 points denotes moderate disease, and ≥11 points signifies severe disease. It is a scale that allows early detection of the increase in the severity of the disease.[1,54]

There is a great emotional and psychological impact due to scarring, a permanent sequel of HS, and the need for further rehabilitation due to the fibrosis. Consequences of the disease include a significant reduction in health-related quality of life (HRQoL), low self-esteem, sleep and sexual dysfunctions, work impairment, social withdrawal and stigmatization, anxiety, depression, and suicide. Because of the profound impact on HRQoL, the use of patient-reported outcomes, such as Dermatology Life Quality Index, is considered essential in the management of HS as well as of pain and pruritus.[2,4,6,7,38,62,66]

In recent years, HS-specific HRQoL instruments, such as HIDRAdisk, HiSQOL and HSQoL-24, have been developed.[32–34] These tools have been validated but there is still a lack of experience of their use. Several treatment agents showed a positive effect on patients' HRQoL and surgery remains a method with a substantial positive effect on HRQoL.[2,4,32–34]

Medical treatment of HS

High-quality randomized clinical trials of HS therapies are scarce. However, medical experience and knowledge about medical treatments are rapidly evolving, leading to the publication of multiple reviews and treatment guidelines for HS. Surgical approaches are also common, but they are beyond the scope of this systematic revision.

Classical medical therapies, including oral antibiotics and topical treatments, are appropriate for the treatment of mild-to-moderate HS. Biologic agents and immunomodulatory therapies, either alone or in combination with conventional drugs or surgery, are recommended when antibiotics are not effective or contraindicated. Table 1 shows the topical and systemic treatments most commonly used for HS.

Table 1. Main topical and systemic treatments for hidradenitis suppurativa.[1,17,29]

Topical and intralesional treatments	Clindamycin Erythromycin Fusidic acid Gentamicin Benzoyl peroxide Resorcinol Adapalene Azelaic acid Intralesional triamcinolone
Oral antibiotics	Tetracyclines Clindamycin + rifampicin Clindamycin + ofloxacin Trimethoprim/sulfamethoxazole Dapsone Ertapenem
Oral retinoids	Acitretin Isotretinoin
Antiandrogens	Metformin Finasteride Ethynilestradiol
Anti-inflammatories and immunosuppressants	Systemic steroids Zinc
Biologics	Adalimumab Infliximab Secukinumab Canakinumab Ustekinumab Etanercept Anakinra Apremilast Golimumab Certolizumab pegol

General measures

Lifestyle interventions

Lifestyle interventions can contribute to a decrease in the frequency of disease flares and reduce pain and irritation at involved areas, and are considered a fundamental part of treatment. The main factors to be addressed are tobacco cessation and weight loss. Adequate diet and mild exercise contribute to weight loss; adaptation of clothing to prevent heating and friction is also advised. Laser hair removal is advised in the disease-prone areas as hair follicles are the initial process culprit.[2,7,10,25,28,32–35,59–60]

Topical treatments

The evidence-based literature available on the use of topical treatments in HS is limited and, for the most part, restricted to retrospective studies and expert opinion.

Topical clindamycin 1% gel or solution is recommended in mild cases with superficial lesions and during flares. Other antibiotics (erythromycin, fusidic acid), benzoyl peroxide, retinoids (adapalene), resorcinol, and intralesional steroids, especially triamcinolone, are recommended.[1,5,9,37,45,56–58]

Systemic treatments

Tetracycline 500 mg twice a day (or doxycycline 100 mg b.i.d.) is recommended as first-line oral treatment for patients with mild to moderate disease for 12–16 weeks. Cotrimoxazole has

been appointed as a suitable option.[1] Next step would be systemic clindamycin 300 mg monotherapy or in association with rifampicin 300 mg for 10 weeks. If lesions are controlled, oral antibiotic treatment should be suspended, and the same antibiotic can be reintroduced later. If clinical response is unsatisfactory, a second scheme of antibiotics is indicated; other treatment modalities should be considered if there is no response or treatment loses its efficacy, or there are contraindications to the second option of antibiotics.[1,9,37,39,45,58] Of note, isotretinoin is not recommended as a therapeutic option for HS; acitretin can be indicated in selected mild cases.[1,5]

Biologic and immunomodulatory agents

Early case reports and case series demonstrated that TNF inhibitors were useful in the treatment of HS.[1,40–43] Two phase III clinical trials, PIONEER I and PIONEER II, showed that adalimumab was an effective treatment for HS.[18,22,27,39–43,59] Clinical trials did not show benefits with the use of etanercept but demonstrated sustained improvement with infliximab.[1,5,9,47–49,64] More recent case reports and small series supported the effectiveness of ustekinumab and secukinumab in the treatment of HS.[1,5,18,39–43,49]

Adalimumab, a recombinant human TNF inhibitor, is the only approved biologic agent indicated for the treatment of moderate-to-severe HS unresponsive or intolerant to oral antibiotics.[5,9,18,22,27,39–43,59,61,66] Long-term use is needed to maintain control of manifestations; safety and efficacy profile of long-term adalimumab is documented.[67–70]

Infliximab is a chimeric mouse/human anti-TNF monoclonal antibody. It is currently used off-label as a second-line biologic treatment in patients with Hurley III stage or HS resistant to adalimumab.[1,9,22,27,36,41–43,51,61,64]

Ustekinumab is a human monoclonal antibody with high affinity for IL-12 and IL-23. The role of the IL-12/23 pathway has been recognized in the pathogenesis of HS. In case reports or case series, ustekinumab has been successful for the off-label treatment of patients who did not respond to adalimumab.[1,23,41,42,51]

Secukinumab is an anti-IL-17A monoclonal antibody that binds to IL-17A, inhibiting the inflammatory cascade. Studies demonstrated the role of the IL-17A pathway in the pathogenesis of HS. Clinical response to secukinumab was successful in the off-label treatment of patients with severe HS who did not respond to previous therapies.[1,10,18,26,49,52,55]

Other immunomodulator agents (e.g. apremilast, etanercept, rituximab, anakinra, canakinumab, certolizumab pegol) have been tested in isolated cases or case series, with variable results.[1,5,9,18,28,29,41–43]

Several new biologics and immunomodulators are under investigation for HS, including bermekimab, bimekizumab, golimumab, guselkumab and risankizumab.[18,42,43,50,51]

Most biologic agents were well tolerated and demonstrated a good safety profile. In general, mild upper respiratory infections were reported as the most common adverse event. Anti-TNF agents require the exclusion of active infections, especially tuberculosis, and vigilance during their use. Treatment with biologic agents can be associated with other modalities such as antibiotics and surgery.

Discussion

Our systematic review synthesizes the data from the most recent (less than 5 years) papers about the medical treatment of HS, including papers from Brazil. The scarcity of high-quality evidence on which to base clinical recommendations, especially regarding treatment strategies for long-term outcomes, was a limitation to the development of this systematic review. However, our framework analysis is a well-adapted methodology to research this complex health issue using specific questions, key themes and a limited time frame.[1,5,9,17,22,33,39,51]

Most evidence to guide management recommendations is based on case reports, case series, small cohort studies and expert opinion. Due to a methodological decision, we did not include surgical treatments in the present review, but it seems important to note that the paucity of solid evidence also applies to surgical approaches for HS.[1,5,16,17,22,33,53,56–59]

There is no single best approach. Medical and surgical therapies are to be used in concert, associated with lifestyle modifications and guided by a multidisciplinary team.

Frequently associated comorbidities include obesity, metabolic syndrome, hormonal disorders, smoking, pyoderma gangrenosum and arthritis; all these conditions should be properly assessed and managed.[1,2,6,7,29,37,39,66]

HS treatment aims to improve a patient's quality of life, relief pain and pruritus, stop disease progression, and control existing lesions.

Topical therapy, as clindamycin, is useful in treating superficial and localized lesions. Resorcinol, azelaic acid and topical retinoids are recommended to treat areas minimizing the appearance of new nodules and improving dyschromic scarring.

Systemic medical therapy aims at controlling nodules and abscesses, and bouts of inflammation. Antibiotics and anti-TNF agents do not induce remission of fistulae, which have to be surgically excised or otherwise destroyed. It remains to be demonstrated whether other new biologic agents have this ability.

As HS is a progressive disease, effective treatment is desirable in the earliest stages to prevent tissue fistulae, tissue destruction, or remodelling and scarring.

First-line systemic therapy includes tetracycline and its derivates or, alternatively, cotrimoxazole for 16 weeks. If control of nodules and abscesses is achieved, medication can be withdrawn. The remaining deep lesions can be infiltrated or

excised during this period or at its end. If control is achieved, topical resorcinol or azelaic acid can be maintained. In case of relapse, the same antibiotic can be reinitiated. Short-term antibiotics are not useful to control HS, only eventual bouts of infection or inflammation.

Second-line antibiotic therapy includes clindamycin, either alone or in combination with rifampin or ofloxacin, for up to 10 weeks.

Other agents, such as immunosuppressants, dapsone, colchicine and oral retinoids, are reported in case reports or small series. Of note, isotretinoin, whilst highly effective in severe acne forms, is seldom effective in HS, not being recommended in guidelines. Acitretin is preferred, albeit in mild cases. Ertapenem is also effective but it is reserved as a third-line option.[17]

A bio-eligible patient is one who does not respond, loses response, has contraindications to antibiotics, and has mild-to-severe HS. The most reliable severity index is the IHS4. Of note, the presence of one fistula is an indication of at least a moderate-to-severe case. An IHS4 index of 4 or more points indicates that the patient is eligible for biologics.[1,2,5,9,17,33,36,61]

Knowledge about the pathophysiology of HS has greatly expanded. Histopathological examination of initial lesions shows terminal follicular hyperkeratosis. Rupture of the follicle initiates an inflammatory reaction, resulting in nodules. The release of the follicular content to the dermis induces an inflammatory reaction with the subsequent development of abscesses. Cells derived from the external root sheath of the hair follicle interact with stromal components resulting in tunnels, sinus tracts and fistulas, fibrosis, scars, and frequent secondary infections.[11–14,16,37]

In recent years, many components of the complex inflammatory response of HS have been better characterized. TNF, IL-17 and IL-12/23 pathways, IL-1, IL-36 and C5a play essential roles in immune dysregulation. T_H17 lymphocytes and neutrophils appear to be the main source of the pro-inflammatory cytokines in the pathogenesis of HS. Pain is one of the most common and debilitating symptoms in patients with HS, along with scarring. Pain may be caused by inflamed nodules, abscesses, neuroinflammation and chronic fibrosis. Recent research has associated HS-related pain with the IL-17 pathway.[2,12–14,21,23,26,35–37]

Due to the extensive available evidence supporting its use, adalimumab is currently the only on-label agent for biologic therapy in moderate-to-severe HS. High-quality trial data for the use of adalimumab suggest that partial or good responders should continue the therapy with periodic assessments.[67–70] Patients who do not respond to treatment, i.e. less than 25% improvement in abscesses and an inflammatory nodule count within 12 weeks, should be eligible to a second biologic agent such as infliximab.[5,9,22,23,34,36,39–43,47,59,61]

Emerging drugs that show promise as options for the treatment of moderate-to-severe HS include IL-1 receptor antagonists, IL-17A inhibitors, IL-12/23 inhibitors and oral phosphodiesterase-4 (PDE4) inhibitors.[10,18,41,50,51]

Montero-Vilchez et al.[23] evaluated the therapeutic outcomes of 10 patients with HS treated with ustekinumab, an IL-12/23 inhibitor. In this case series, an improvement in HS-PGA was observed in 70% of patients with an 80% improvement on the pain scale. According to the authors, these outcomes suggest that ustekinumab may be an effective and safe option for patients with HS who fail to respond to first-line therapies.[23]

Casseres et al.[39] reported an open-label trial of secukinumab, an IL-17 inhibitor, in the treatment of HS. They enrolled 20 patients with moderate-to-severe HS, defined as a Hurley stage II or III, including 6 patients with previous anti-TNF exposure. The primary endpoint was to determine the proportion of patients who achieved an HS clinical response (HiSCR) after 24 weeks of secukinumab. Overall, 70% of all patients achieved HiSCR by week 24, including 5 out of the 6 patients with prior anti-TNF exposure. Secukinumab was well tolerated and no serious adverse events were reported.[39]

Thorlacius et al.[49] reported a case of a 47-year-old man with severe HS lesions and widespread disease who had not previously experienced sustained benefit from different medical treatments. After 12 weeks of treatment with secukinumab, the number of HS lesions reported by the patient was significantly reduced, whilst his pain and handicap scores showed important improvements. The authors suggested that IL-17 blockade may provide therapeutic benefits in the treatment of HS.[49] According to Wu et al.,[26] other IL-17 inhibitors, such as brodalumab, are being studied as a third-line option for the treatment of resistant, severe HS.

The various clinical endpoints and measurement scores used in different studies or case series to assess the effectiveness of both conventional and biologic drugs potentially complicate direct comparison between agents.[9,41,39,53]

Limitations

A limitation of our systematic review is precisely the thematic qualitative nature, where relevant literature was selected and interpreted based on the knowledge and experience of the authors. However, the framework analysis is a well-fitted methodology for investigating such a complex and multifaceted disease, where evidence-based data are scarce and most information comes from isolated case reports, case series, small observational studies, clinical experience and expert opinion.

Conclusion

HS is a complex chronic skin disease that has a profound impact on the quality of life of affected individuals. Advances in the understanding of its pathogenesis are considerable and have confirmed its immune and inflammatory background. Early diagnosis and multimodal interventions on comorbidities can

improve the course of the disease. Therapy with antibiotics and immunomodulators promotes a better systemic control of the inflammation, reducing symptoms and complications.

Our results show that mild-to-moderate HS may be successfully treated with oral antibiotics, topical therapy and lifestyle modifications. However, moderate-to-severe HS remains refractory to conventional treatments. Biologics, indicated for moderate-to-severe cases that failed conventional treatment, have been shown to be effective and safe in HS. The use of different clinical endpoints and measurement scores makes comparison difficult.

There is still a paucity of high-level evidence for the medical management of HS in terms of clinical studies and data quality. Nonetheless, our systematic literature review retrieved valuable, useful and up-to-date information on the current treatment of HS.

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