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Review

Golimumab and certolizumab pegol for the treatment of hidradenitis suppurativa: a literature review and future perspective

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***Abstract*:** Hidradenitis suppurativa (HS) is an inflammatory skin condition with an underlying inflammatory process. Due to the limited efficacy of available treatments, HS remains a therapeutic challenge. The safety and efficacy of tumor necrosis factor-α (TNF-α) inhibitors, adalimumab, infliximab, and etanercept, are well studied in this patient population, and in some cases, HS was unresponsive to them. In recent years, evidence has been growing regarding the application of other anti-TNFs, including certolizumab pegol (CPZ) and golimumab. We sought to evaluate the overall safety and efficacy of golimumab and CPZ in the management of HS. A comprehensive search was performed on the PubMed, Scopus, Web of Science, and Ovid Embase databases, as well as the Google Scholar search engine from initiation to 31 August 2023. A total of nine and four studies used CPZ and golimumab to treat HS, respectively. Individuals with concomitant inflammatory immune-mediated diseases, pregnant females, and patients who were refractory to previous treatments achieved a Hidradenitis Suppurativa Clinical Response following CPZ administration. Also, golimumab showed promise in treating recalcitrant HS after the failure of other treatments, such as adalimumab and anti-interleukin-1. CPZ and golimumab can be efficacious treatment options for moderate-to-severe HS, especially in patients who are unresponsive to other TNF inhibitors, such as adalimumab.

Keywords: acne inversa, certolizumab pegol, golimumab, hidradenitis suppurativa, TNF-α inhibitors, tumor necrosis factor-α

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Introduction

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic inflammatory cutaneous disease mostly seen in apocrine gland-rich body sites like the axilla, groin, and anogenital area.[1,2] The condition can manifest as recurrent painful nodules, fistulas, abscesses, and even keloid scars, leading to severe impairment of patients' quality of life and self-esteem.[3] HS commonly emerges during the third and fourth decades of life,[2] and its global prevalence varies between 0.00033% and 4.1%, with European and US populations notably exhibiting a relatively higher prevalence rate, ranging from 0.7% to 1.2%.[4] The gender distribution of HS exhibits regional disparities.[5] In North America and Europe, females are three times as likely to experience HS as males. Conversely, in South Korea, males are twice as likely to be affected by HS compared to females.

To date, the exact pathogenesis has not been determined. However, HS is likely a multifactorial disease that primarily presents when hair follicles are occluded following hyperkeratinization or hyperplasia, resulting in cyst formation,[6] which is followed by cyst rupture with consequent inflammation accompanied by both innate and adaptive responses. Tumor necrosis factor-α

(TNF-α) is found to be the primary trigger of the inflammatory response.[7] Accordingly, serum and lesional skin levels of TNF-α and other inflammatory cytokines, such as interleukin (IL)-1β, IL-10, and IL-17, were higher in HS patients than in healthy individuals. Furthermore, remarkably elevated frequencies of TNF-producing T cells in HS skin suggest that TNF is a striking target in HS.[8] In spite of the implication of multiple inflammatory cytokines in HS pathogenesis, anti-TNF-α therapy holds promise in HS management as it decreases the majority of these pro-inflammatory cytokines.[7] Several TNF-α inhibitors are currently used in treating HS, including adalimumab, infliximab, and etanercept.[3,9,10] Adalimumab is the first and only Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved TNF-α inhibitor for HS treatment.[3,11] Additionally, many studies have assessed the efficacy of infliximab and etanercept on HS patients over the recent years.[12] Nonetheless, the outcomes associated with these medications did not yield favorable results in some cases.[13,14]

In recent years, there has been an increasing body of evidence concerning the use of unconventional therapies for HS.[15] In refractory cases, alternative anti-TNFs, including certolizumab pegol (CPZ) and golimumab, may be efficacious. CPZ has already been FDA-approved for psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.[6] Given that CPZ does not pass through the placenta, it represents a viable treatment option for pregnant individuals with HS or patients who have not responded to previous treatment options. Moreover, golimumab is an anti-TNF-α antibody, which is previously FDA-approved for rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis,[3] which can be potentially utilized in HS cases refractory to biologic agents.[16] Of these, we aimed to evaluate the efficacy and safety of CPZ and golimumab in treating HS patients, particularly among cases unresponsive to other treatments.

Systematic search and methodology

We conducted a comprehensive search through four databases: PubMed, Web of Science, Ovid Embase, and Scopus, up to 31 August 2023, using the relative search terms hidradenitis suppurativa OR acne inversa AND certolizumab pegol OR golimumab OR tumor necrosis factor OR TNF OR anti-TNF. Clinical studies (clinical trials, observational studies, case series, and case reports) with available English full texts were included in this study. The eligible source populations were individuals of any age and gender treated with CPZ or golimumab for HS. Reviews, guidelines, experimental studies (*in vitro*/*ex vivo* or animal studies), and studies utilizing other anti-TNF agents (adalimumab, infliximab, and etanercept) were excluded. As a result, 13 studies were selected, including 10 case reports and 3 cohort studies. Nine and four studies reported the application of CPZ and golimumab in HS, respectively. Thirteen studies assessed CPZ and golimumab, TNF inhibitors that are not approved by the FDA or EMA, to treat HS in a total of 39 patients. The results of the included studies are demonstrated in Table 1.

CPZ in the treatment of HS

CPZ is a recombinant humanized antibody against TNF-α.[27] It is a potential therapeutic option for treating immune-mediated inflammatory diseases like plaque psoriasis. Nine studies reported 22 patients with HS who were treated with CPZ. A retrospective cohort study by Esme *et al.*[9] evaluated the efficacy of CPZ as a therapeutic option for 11 Hurley stage III HS participants who failed to respond to adalimumab. In six patients (54.5%), Hidradenitis Suppurativa Clinical Response (HiSCR) was gained by week 12; two lost responses by week 24 despite continuing treatment (HiSCR at week 24: 33.3%). A significant decline in Dermatology Life Quality Index (DLQI) and International Hidradenitis Suppurativa Severity Score System (IHS4) scores was also found in the patients at weeks 12 and 24 compared to baseline. Generally, CPZ was tolerated well (81.8%, $n=9$) by the patients. Nevertheless, severe adverse cutaneous maculopapular drug reactions in the first month and severe nausea and low blood pressure following the third dose led to treatment discontinuation in two participants. Another cohort study by Sand and Thomsen[10] assessed the use of TNF-α inhibitors in 29 individuals with HS, two of whom received CPZ. After an average of 13 months, CPZ appeared ineffective since neither patient experienced symptom resolution.

Table 1. Characteristics included studies of golimumab and CPZ in the treatment of hidradenitis suppurativa patients.

Study ID	Design of study	Sample size	Gender ratio (%F:M)	Age mean (range)	Past medical history and comorbidities	Condition(s)	Disease duration (year)	Previous treatments	Treatment(s) of study	Outcome measurement	Efficacy	Safety and adverse effects	Relapse	Follow-up evaluation
Esme *et al.*, 2022[9]	Cohort study	11	M	42	Pt1: myocardial infarction; Pt3: CD; Pt4: FMA, RA; Pt6: Insulin resistance; Pt7: Coronary artery disease; Pt11: Fournier's gangrene	Hurley stage III	Pt1: 30 Pt2: 7 Pt3: 2 Pt4: 35 P5: 8 Pt6: 4 Pt7: 29 Pt8: 8 Pt9: 6.5 Pt10: 4 Pt11: 20	Pt1: adalimumab, infliximab, ustekinumab, secukinumab; Pt 2,3,5,6,7,8,9,10: adalimumab; Pt 4: adalimumab, infliximab, secukinumab, Kineret; Pt 11: adalimumab, secukinumab	CPZ	IHS4, HiSCR, AN50, AN75, AN100	6 of 11 patients achieved HiSCR by week 12. Two of the six responders lost their HiSCR response by week 24. Median values of IHS4 scores at week 0 were 24 (min–max: 20–48), at week 12 was 12 (min–max: 7–26), and at week 24 was 12 (min–max: 3–24). IHS4 decreased at weeks 12 and 24, showing a significant difference compared to the baseline significant difference between weeks 12 and 24. The rates of AN50, AN75, and AN100 were 54.5% ($n=6$), 36.4% ($n=4$), and 0% ($n=0$) at week 12, at week 24 were 36.4% ($n=4$), 9% ($n=1$), and 0% ($n=0$), respectively. Median values of DLQI scores at week 0 were 27 min–max: 20–29, week 12 was 16 (min–max: 12–29), and week 24 was 15 (min–max: 10–30; IQR: 13). DLQI decrease between weeks 12 and 24 showed a significant difference compared to the baseline. No significant difference was seen between weeks 12 and 24.	Well tolerated (81.8%, $n=9/11$). Treatment discontinuation in two patients owing to severe adverse cutaneous maculopapular drug reaction in the first month, in addition to severe nausea and low blood pressure after the third dose of drug administration. A 57-year-old patient with a history of FMA and RA achieved HiSCR response at weeks 12 and 24 and died in the intensive care unit due to PCR-confirmed COVID-19 after 8 months of treatment.	NA	Follow-up after 24 weeks

(Continued)

Table 1. (Continued)

Study ID	Design of study	Sample size	Gender ratio (%F:M)	Age mean (range)	Past medical history and comorbidities	Condition(s)	Disease duration (year)	Previous treatments	Treatment(s) of study	Outcome measurement	Efficacy	Safety and adverse effects	Relapse	Follow-up evaluation
Sand and Thomsen, 2015[10]	Cohort study	Two (total of 29 patients with HS, two receiving certolizumab)	NA	NA	NA	NA	NA	Antibiotics, triamcinolone, isotretinoin, dapsone	CPZ 200 mg twice monthly for an average of 13 months (range 1–50 months) in combination with adalimumab ($n = 1$) and infliximab ($n = 1$)	Clinical signs and symptoms	Both patients with no response to therapy	No AEs	NA	NF
Repetto *et al.*, 2022[17]	Case report	2	F	Pt1: 30 Pt2: 35	Psoriasis in both patients	Bilateral axillary and inguinal	NA	Adalimumab 40 mg weekly for approximately 2 years	CPZ 200 mg SC administrated for 3 months	IHS4, clinical signs and symptoms, HiSCR	After 3 months, a great improvement was observed in both patients without evident inflamed lesions referable to HS, and multiple scars on the axilla bilaterally without inflamed nodules were observed. HiSCR: achieved for both. IHS4: Pt 1 (8–3), Pt2 (11 to 2)	NA	NA	NF
Melgosa Ramos *et al.*, 2022[18]	Case report	2	Pt1: F (pregnant) Pt2: F	Pt1: 33 Pt2: 34	Pt1: obesity, CD; Pt2: psoriasis, arthralgias, hypothyroidism, membranous nephropathy, chronic spontaneous urticaria	Pt1: Hurley stage II; Pt2: Hurley stage III	NA	Pt1: adalimumab Pt2: methotrexate, adalimumab, secukinumab	CPZ 400 mg SC on the week 0, 2, and 4, and then 200 mg every 14 days for maintenance	IHS4, HiSCR, control of the other inflammatory immune-mediated comorbidities	Reaching HiSCR after 16 weeks and 24 weeks; Pt1: IHS4 dropped from 12 to 0, maintaining Crohn's disease control and without suffering obstetric problems; Pt2: IHS4 dropped from 6 to 0, reduced methotrexate dosage from 12.5 to 7.5 mg weekly, maintaining psoriasis control, improving polyarthralgia	Neusa	No relapse	NF
Wohlmuth-Wieser and Alhusayen, 2021[19]	Case report	1	F (pregnant)	34	Obesity	Hurley stage III, groin and buttocks	22	Repeated surgeries, adalimumab, clindamycin, rifampin	CPZ 400 mg SC every 2 weeks starting at 19 weeks of gestation, increased to 400 mg weekly at 32 weeks of gestation	HiSCR, IHS4, clinical symptoms	HiSCR 50 was achieved after 8 weeks, with significant improvement in groin and gluteal region after 8 and 16 weeks; IHS4 dropped from 44 to 9 after 16 weeks	Well-tolerated without any side effects	Worsening pain and one new abscess after 8 weeks	Follow-up after delivery (21 weeks of treatment), switching back to adalimumab

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Table 1. (Continued)

Study ID	Design of study	Sample size	Gender ratio (%F:M)	Age mean (range)	Past medical history and comorbidities	Condition(s)	Disease duration (year)	Previous treatments	Treatment(s) of study	Outcome measurement	Efficacy	Safety and adverse effects	Relapse	Follow-up evaluation
Esme *et al.*, 2021[20]	Case report	1	M	43	Pilonidal sinus and Fournier's gangrene	Hurley stage III; Bilateral axillary areas, intergluteal sulcus, and especially the right gluteal	15	Methotrexate, adalimumab, secukinumab, antibiotics, and retinoids	CPZ Similar dosing to psoriasis patients: 400 mg every other week	Sartorius score, VAS, DLQI, HiSCR, clinical symptoms	Sartorius, 10-point VAS, and DLQI scores regressed from 171 to 105, 9/10 to 3/10, and 27 to 19, respectively; reaching HiSCR after 3 months, diminished inflammation and discharge on the right gluteal, right axilla, and left axilla	NA	NA	NF
Holm *et al.*, 2020[21]	Case report	1	M	57	DM2, HTN, HLP	Hurley stage III Multiple painful inflammatory nodules, abscesses, and sinus tracts in both axillae and groins.	18	Topical azelaic acid and clindamycin, systemic lymecycline, rifampicin and clindamycin, acitretin, dapsone, adalimumab, ustekinumab, ixekizumab, secukinumab, etanercept, surgical incision, laser surgery	CPZ 400 mg every 2 weeks for 1 month, 200 mg every week for 20 months	DLQI, VAS, HSS, clinical signs, and symptoms	Good symptom control with less suppuration, visible inflammation, and overall well-being with DLQI (25 to 11), VAS (10 to 5), HSS (133 to 75)	NA	NA	NA
Tampouratzi *et al.*, 2019[22]	Case report	1	F	27	Psoriasis vulgaris covering the head, trunk, and lower limbs, psoriatic arthritis with axial joint involvement	Hurley stage II; axillary	2	Methotrexate, apremilast	CPZ 400 mg every 2 weeks	IHS4, DLQI, clinical signs, and symptoms	Improvement of HS and psoriasis after 12 and 8 weeks: IHS4 dropped from 10 to 1, DLQI dropped from 21 to 2	NA	No relapse	Follow up after 3 months complete control of disease, continued treatment 9 months after
Abad *et al.*, 2019[23]	Case report	1	M	53	Smoking, obesity	Severe HS axillary and genital area	15	Antibiotics, adalimumab, and infliximab	CPZ 400 mg as 2 injections SC of 200 mg each on weeks 0, 2, and 4, a maintenance dose of 400 mg every 4 weeks	Clinical signs and symptoms, cutaneous ultrasound	Complete resolve of nodules and abscesses, even in the axillary and genital area, an important improvement in cutaneous ultrasound after 3 months	No AEs	No relapse	Follow-up after 10 months, still under treatment with CPZ, no subjective or laboratory adverse reactions

(Continued)

Table 1. (Continued)

Study ID	Design of study	Sample size	Gender ratio (%F:M)	Age mean (range)	Past medical history and comorbidities	Condition(s)	Disease duration (year)	Previous treatments	Treatment(s) of study	Outcome measurement	Efficacy	Safety and adverse effects	Relapse	Follow-up evaluation
Melendez-Gonzalez *et al.*, 2021[16]	Cohort study	13	F: 92.3% M:7.7%	41.5 ± 11.6	Obesity (*n* = 13), Smoking (*n* = 13), IBD (*n* = 2), PG (*n* = 2), SAPHO syndrome (*n* = 2), PASH syndrome (*n* = 1)	Hurley Stage II (*n* = 2) and III (*n* = 11)	NA	Adalimumab (*n* = 12), Infliximab (*n* = 13), oral antibiotics (*n* = 2), IV antibiotics (*n* = 3), methotrexate (*n* = 6), oral steroids (*n* = 3), isotretinoin (*n* = 3)	Golimumab median 36 weeks of intravenous golimumab treatment at a dose of the higher of either 2 mg/kg or 200 mg, at week 0, week 2, and every 4 weeks	HiSCR, IHS4, DLQI, pain score, HS-PGA, ESR, CRP, hematocrit	8 of 12 achieved HiSCR. IHS4 among achieving HiSCR subjects decreased significantly (median change 9 from 13 to 2). The final score fell from the severe to mild range. HS-PGA score decreased from moderate to mild severity. No significant change in pain score, DLQI, hematocrit, ESR, and CRP	Well-tolerated AEs: one case mild throat pruritis; one case *Clostridium difficile* colitis	NA	NF
Ramos *et al.*, 2022[24]	Case report	2	F	Pt1: 44 Pt2: 33	Pt1: SAPHO syndrome Pt2: RA	Hurley stage III Pt1: axillary and inguinal folds; Pt2: inguinal, axillary, and inframammary folds	NA	Pt1: methotrexate, antibiotics, adalimumab Pt2: methotrexate, antibiotics, adalimumab, ustekinumab	Golimumab 200 mg SC week 0, 100 mg week 2, 100 mg monthly	IHS4, HiSCR	Joint control and reaching HiSCR after 36 weeks; Pt1: IHS4 dropped from 12 to 2; Pt2: IHS4 dropped from 15 to 4	NA	NA	NF
Tursi, 2016[25]	Case report	1	F	42	UC, PV	Hurley stage II	NA	Mesalazine, oral prednisone, dapsone	Golimumab 200 mg SC followed by 100 mg every 4 weeks, together with amoxicillin-clavulanate 2 g/day for 2 weeks	Clinical signs and symptoms	Disappearance of dermatological and oral lesions within 2 months of treatment	NA	No relapse	Follow-up after 4 months still under treatment with golimumab; No relapse in oral and dermatological lesions, and clinical remission of UC
Van der Zee and Prens, 2013[26]	Case report	1	F	51	Smoking, DM2, and psoriatic arthritis	Hurley stage III groins, buttocks, and perianal region	22	Antibiotics, total excision of the skin of both axillae resulting in total clearance of HS in those areas, adalimumab, methotrexate, anakinra	Golimumab 50 mg SC once a month monotherapy and in combination with oral rifampicin 300 mg twice a day and oral clindamycin 300 mg twice a day	PGA	Golimumab: PGA changed from 6 to 8 after 8 months, good control of arthritis Golimumab + clindamycin-rifampin: PGA dropped from 8 to 7 after 4 months	NA	No relapse	Follow-up after 24 months, planned for surgical excision of all affected skin due to the failure of several treatments

AEs, adverse events; AN, inflammatory nodule; AN100, 100% reduction in total AN count from baseline; AN50, 50% reduction in total AN count from baseline; AN75, 75% reduction in total AN count from baseline; BD, Behçet's disease; CD, Crohn's disease; COVID-19, Coronavirus Disease 2019; CPZ, certolizumab pegol; CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; G, Group; hBD-2, human beta-defensin-2; HiSCR, Hidradenitis Suppurativa Clinical Response; HLP, hyperlipidemia; HS, hidradenitis supporativa; HS-PGA, Hidradenitis Suppurativa Physician's Global Assessment Scale; HSSA, hidradenitis suppurativa symptom assessment; HTN, hypertension; IHS4, Hidradenitis Suppurativa Severity Score System; IBD, inflammatory bowel disease; IV, intravenous; IQR, interquartile range; NA, not applicable; NF, no follow-up; PASH, pyoderma gangrenosum, acne, and hidradenitis suppurativa; PCR, polymerase chain reaction; PG, pyoderma gangrenosum; PGA, global physician assessment; Pt, patient; PV, pyostomatitis vegetans; RA, rheumatoid arthritis; SAPHO Syndrome, synovitis, acne, pustulosis, hyperostosis, osteitis; SC, subcutaneously; SLE, systemic lupus erythematosus; UC, ulcerative colitis; VAS, Visual Analog Scale.

Four case reports assessed the effectiveness of CPZ in pregnant or childbearing females with or without other comorbidities.[17–19,22] Repetto *et al.*[17] reported two females with bilateral axillary and inguinal HS and concomitant psoriasis switching from adalimumab to CPZ. Both patients experienced tremendous improvement and reductions in IHS4 and HiSCR achievement following 3 months of treatment. Further, Melgosa Ramos *et al.*[18] found that CPZ resulted in a significant drop in IHS4, as well as reaching and maintaining HiSCR after 16 and 24 weeks, respectively, in two female patients. Thus, CPZ can be considered a first-line treatment or an alternative option after adalimumab failure due to its ability to manage HS and co-occurring inflammatory immune-mediated diseases in patients.

Moreover, Wohlmuth-Wieser *et al.*[19] utilized CPZ to treat a pregnant patient. Despite worsening pain and one new abscess after 8 weeks, the patient attained HiSCR. A reduction in IHS4 and improvement in the groin and gluteal region were also reported. Likewise, the administration of CPZ was beneficial for another female patient, as reported by Tampouratzi *et al.*[22] The patient experienced an impressive reduction in IHS4 and DLQI and complete control of her HS and psoriasis at three 3-month follow-ups. In three case reports, CPZ had acceptable efficacy and safety in managing HS patients who were also unresponsive to several previous treatments.[20–22] Assessing the clinical symptoms, utilizing cutaneous ultrasound, and evaluating different scores such as the sartorius score, visual analog scale, and DLQI demonstrated the patients' responsiveness to CPZ.

Golimumab in the treatment of HS

The monoclonal antibody golimumab targets and neutralizes TNF-α.[28] Golimumab has been approved for managing immune-related diseases, including RA, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis, and ulcerative colitis. Golimumab was used to manage 17 other patients who did not benefit from several previous treatments, such as adalimumab, infliximab, ustekinumab, anakinra, and methotrexate. In a retrospective cohort study, 13 Hurley stage II/III patients received a median of 36 weeks of golimumab treatment at a dose higher than 2 mg/kg or 200 mg at Week 0, Week 2, and every 4 weeks.[16] HiSCR was achieved in six out of nine cases, with data available for HiSCR calculation. A significant reduction was observed in IHS4, with a change in the median score of 9 points and a drop from the severe to mild range in the final score. Also, the hidradenitis suppurativa physician's global assessment (HS-PGA) score decreased from moderate to mild severity. Besides, most clinical and laboratory assessments, including pain score, DLQI, Hematocrit, erythrocyte sedimentation rate, and C-reactive protein, did not show remarkable improvement due to the limited cohort size. Golimumab was claimed to be well-tolerated with no severe adverse events. Meanwhile, two patients experienced mild throat pruritis and *Clostridium difficile* colitis.

The outcome of case reports revealed mixed results regarding the efficacy of golimumab. In a number of cases, golimumab was successful in treating HS associated with other diseases and comorbidities. Subcutaneous injection of 200 mg golimumab on week 0, followed by 100 mg on week 2 and then 100 mg monthly in two patients with SAPHO syndrome and RA, led to a decrease in IHS4 as well as reaching joint control and HiSCR after 36 weeks.[24] In a patient with pyostomatitis vegetans and ulcerative colitis, the administration of golimumab and amoxicillin–clavulanate resulted in clinical remission of ulcerative colitis and the disappearance of dermatological and oral lesions within 2 months of treatment.[25] Nonetheless, golimumab 50 mg once weekly, both alone and in combination with rifampicin and clindamycin, worsened the HS symptoms of an individual with Hurley stage III HS with groins, buttocks, and perianal region involvement and psoriatic arthritis.[26] Having failed to respond to adalimumab, anakinra, and golimumab treatments, the patient underwent radical excision of the inflammatory lesions and fistulas.

Discussion

HS is a chronic skin condition identified by the formation of painful nodules, abscesses, and sinus tracts in intertriginous body areas, significantly reducing the patient's quality of life.[29] In HS, follicle occlusion is the primary mechanism leading to intradermal follicular cyst formation and rupture.[30] In addition to the chemotactic inflammatory response of neutrophils and lymphocytes, immunological deficiencies are pivotal in HS pathogenesis.[3] By details, TNF-α facilitates cell

migration, as well as endothelial activation, eventually leading to engaging other inflammatory cells such as neutrophils, macrophages, and plasma cells.[1] Also, TNF-α elevates the ratio of T helper (Th) 17 to regulatory T-cells following Th17 polarization reinforcing, which is a significant factor for disease onset in lesion-involved tissue.[3,8,30] Likewise, TNF-α is involved in the mammalian target of rapamycin (mTOR) signaling pathway, directly associated with disease severity.[3] Further, TNF-α may disrupt insulin signaling on adipocytes and muscle cells, contributing to increased fasting blood sugar and insulin resistance commonly observed in HS patients.[31] Anti-TNF-α therapy could potentially decline mTOR1 expression, the ratio of Th17 to regulatory T-cells, and IL-17-producing T-cells, which subsequently decrease the expression of IL-22, interferon-gamma, and IL-2.[8,31] Accordingly, the role of immunomodulatory drugs, particularly TNF-α inhibitors, for targeted therapy is enhanced compared to other treatment options for HS, which is known to be challenging to manage because of the wide range of severity and clinical manifestations.[3] However, due to the recent increase in the use of biologics in treating HS, the incidence of paradoxical reactions has been growing.[32]

Several TNF-α inhibitors, including adalimumab, infliximab, and etanercept, have been investigated in the treatment of HS.[33] To date, adalimumab has been the only FDA- and EMA-approved biologic agent for moderate-to-severe HS.[34] Adalimumab is a fully human recombinant IgG1 monoclonal antibody binding soluble and transmembrane TNF-α with high affinity and specificity. Two phase III multicenter, double-blind, placebo-controlled studies (PIONEER I and PIONEER II) with a population of 633 HS patients demonstrated that 41.8% and 58.9% achieved HiSCR after 12 weeks of treatment.[11] Aside from the branded version of adalimumab, several biosimilars are currently available.[35] However, further investigations are mandatory to indicate the pharmacokinetic similarity, formulation differences, efficacy, safety, and immunogenicity of adalimumab biosimilars.[36]

Infliximab is another TNF-α inhibitor, a chimeric mouse/human IgG1 monoclonal binding to transmembrane and soluble TNF-α with high affinity. Evidence regarding its efficacy is scarce compared to adalimumab; however, infliximab demonstrated effectiveness in HS treatment according to randomized controlled trials, open-label trials, as well as retrospective cohort studies.[14] The efficacy of infliximab can also be explained by its dosing flexibility.[37] Despite showing favorable results, these TNF-α blockers' long-term outcome was variable in HS patients. Etanercept is another fully human recombinant molecule containing two soluble TNF receptor subunits (p75) fused to the human IgG1 fragment crystallizable (Fc) portion. As opposed to adalimumab and infliximab, the administration did not reveal significant efficacy in improving HS, according to a phase II placebo-controlled study.[13]

Following the administration of TNF-α inhibitors, a number of cases of paradoxical immune-mediated diseases and skin reactions, such as psoriasis, have been reported.[32] Additionally, anti-TNFs are represented as the most reported biologics associated with the incidence of paradoxical HS. Patients with paradoxical reactions may benefit from cessation of anti-TNF treatment and receiving additional medication. Hence, a deeper understanding of the inflammatory processes in HS and novel immunomodulators, including IL-17 inhibitors, IL-23 inhibitors, Janus kinase inhibitors, and spleen tyrosine kinase inhibitors, paves the way for a great deal of hope for the patients.[38,39] Recently, the FDA has approved secukinumab, an IL-17 inhibitor, to treat adults with moderate-to-severe HS.[40]

In recent years, evidence regarding the off-label use of other anti-TNFs in HS has been growing since the outcome of the previous options was not satisfactory in all cases.[9,16] Due to their immunogenicity, anti-TNF-α agents may induce the production of antidrug antibodies, resulting in drug failure. In this group of patients, disease control can be achieved by either increasing the current anti-TNF-α dose or switching it to another agent, such as a second TNF-α blocker.[9]

CPZ and golimumab are two anti-TNF-α agents administered in small numbers of patients and showed acceptable efficacy and safety in treating recalcitrant HS.[9,16,20,23,24] Conducting clinical trials and investigations in larger populations is warranted to evaluate the effectiveness and characterize the adverse reactions in larger populations. Moreover, a head-to-head comparison of these drugs and adalimumab in large-scale studies is necessary to ascertain the clinical benefit and safety of switching to another TNF inhibitor

in HS.[9] As of yet, only a head-to-head comparison of CPZ and adalimumab was performed in the RA population by Smolen *et al.*[41] According to the results of this study, about 60% of cases that failed to respond to either of these two drugs could achieve retreatment control by being switched to the other anti-TNF-α agent without a washout period.

CPZ is a pegylated humanized monoclonal anti-TNF-α blocker that, unlike other TNF-α inhibitors, does not cross the placenta, and this feature may relate to the absence of an Fc region, a factor implicated in placental transfer, due to pegylation.[19] It is imperative to note that the safety profile of CPZ during pregnancy has been validated. According to the largest cohort of CPZ-exposed pregnant women, CPZ has not been associated with an increased risk of fetal death and anomalies compared to the general population.[42] Therefore, CPZ can be offered as a potential alternative for HS management in women during pregnancy age. Furthermore, CPZ has been approved for a number of immune-mediated inflammatory conditions and, thus, can be offered in HS patients who suffer from coexisting comorbidities, such as psoriasis, arthritis, inflammatory bowel disease, or spondyloarthropathy.[18,21,22] Based on the current reports, HS and the very conditions often relapse concurrently, and their symptoms also ameliorate with the same treatment tool. Choosing a proper treatment with an optimal dose for both HS and the coexisting diseases should be considered. For instance, the use of anti-IL-17 agents in patients with coexisting HS and inflammatory bowel diseases may exacerbate the condition.[9] In these cases, administering CPZ as a first-line treatment or an alternative to adalimumab resulted in control of the symptoms.[9,18] Moreover, the effective dose of CPZ was 400 mg in weeks 0, 2, and 4, and afterward, 200 mg every 14 days for maintenance, which was the same dose prescribed for psoriasis. Because of the higher level of inflammation in HS, however, the psoriasis dosing regimen might not be enough in these patients. Further experiments are obligatory to assess the dose-response and injection frequency of CPZ for HS.

Golimumab is another fully humanized TNF-α blocker that exhibits a higher affinity for transmembrane and soluble TNF-a receptors than adalimumab and infliximab.[16] Despite showing efficacy in the treatment of RA, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, the evidence regarding the effect of this agent on HS management was contradictory.[16,24–26] This might be due to the variety of drug doses and the administration routes.[16] In detail, it has been suggested that a higher dose than that currently approved for other complications can be effective in HS conditions. Besides, golimumab can be considered in severe HS with comorbid pyostomatitis vegetans, RA, SAPHO syndrome, and psoriatic arthritis.[24–26] As a result of the strong correlation between HS and concomitant immune-mediated diseases, the optimal management of both conditions can be achieved by controlling the existing inflammatory pathways.

In summary, CPZ and golimumab were found to be efficacious and tolerable in treating HS. However, no clinical trials have been conducted to date, and a high level of evidence regarding the efficacy of the aforementioned biologics is still lacking. More clinical investigations with long-term follow-ups are mandatory to evaluate the comparative effectiveness of biologics, including anti-TNF agents, in the management of HS and to gain a better insight into the pathogenesis and subtypes of HS.

Conclusion

Challenges in the management of HS and the limited efficacy of existing therapeutic modalities led to the off-label use of many biologics to fulfill the unmet need. CPZ and golimumab are two types of TNF-α blockers that may contribute to a level of improvement in HS and can be used as an alternative in patients who were unresponsive to adalimumab. CPZ and golimumab also resulted in the alleviation of the concomitant immune-mediated diseases in HS patients. Moreover, CPZ can be considered a safe management option for HS during pregnancy as it lacks active placental transfer. However, further investigations, mainly clinical trials with larger sample sizes, are suggested to determine the effectiveness and safety of these therapeutic tools.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Author contributions
Amirhossein Heidari: Conceptualization; Data curation; Project administration; Validation; Writing – original draft; Writing – review & editing.

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Appendix

Abbreviations

CPZ	certolizumab pegol
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
Fc	fragment crystallizable
FDA	Food and Drug Administration
HiSCR	hidradenitis suppurativa clinical response
HS	hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa Physician's Global Assessment
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
mTOR	mammalian target of rapamycin
RA	rheumatoid arthritis
Th	T helper
TNF-α	tumor necrosis factor alpha