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Interferon-Gamma (IFN-γ) is Elevated in Wound Exudate from Hidradenitis Suppurativa

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Abstract

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease of apocrine glands which affects 1% to 4% of young adults. The purpose of this study was to investigate inflammatory cytokines in effluent from HS lesions and to identify potential local drivers of inflammation in HS.

Wound fluid specimens from HS patients (n=8) and age-matched chronic wound patients (n=8) were selected for analysis. The Hidradenitis Suppurativa Score (HSS) was used to determine extent of HS activity. Cytokine analysis was conducted using Meso Scale Discovery cytokine and proinflammatory panels.

Interferon-gamma (IFN-γ) was significantly elevated in the HS effluent compared to chronic wounds (1418 ± 1501 pg/ml compared to 102.5 ± 138 pg/ml, p 0.027). HS effluent also had significantly higher levels of TNF-β (9.24 ± 7.22 pg/ml compared to 1.65 ± 2.14 pg/ml, p 0.03). There was no significant difference in any other cytokines. There was no significant difference in demographics in the HS compared to chronic wound cohorts. Mean HSS in the HS cohort was 68.88 (SD ± 41.45).

In this proof of concept pilot study, IFN- γ was significantly elevated in HS effluent. TNF-β/LT-α levels were also elevated in HS, although the levels were more modest. Further studies should focus on molecular drivers of tissue injury in HS, and the relationship between HS effluent cytokine profile and disease activity.

Keywords

Wound; Hidradenitis Suppurativa; Ulcer; Cytokine; IFN-γ; Wound fluid; wound effluent

Introduction

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease for which there is currently no known treatment or cure (Jemec 2012). Patients with HS develop debilitating,

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recurrent, inflammatory nodules, sinus tracts and abscesses around apocrine glands. Population-based studies suggest the prevalence of HS ranges from 1% to 4% in young adults (Esmann, Dufour et al. 2010, Cosmatos, Matcho et al. 2013, Vazquez, Alikhan et al. 2013). Women are more commonly affected than men (female: male ratio 3:1), and the disease is more common in African Americans than Caucasians. Smoking and obesity are strongly associated with disease activity (Hessam, Sand et al. 2015). Despite the prevalence of this condition, many patients experience delays in diagnosis.

Until now, a lack of understanding of the mechanistic drivers of HS has been a critical roadblock to developing new therapies. Research to date suggests that HS is a multifactorial disease centered on the hair follicle (Laffert, Helmbold et al. 2010, Danby, Jemec et al. 2013), but it is not known whether the primary driver of disease activity is the host innate or adaptive immune response (Kelly, Sweeney et al. 2014), defective keratinocyte structure or function, or the microbial environment in the hair follicle and apocrine gland (Jahns, Killasli et al. 2014). Histopathological studies suggest HS patients have a defect of keratinocyte shedding resulting in blockage of the hair follicle, buildup of secretions in the apocrine glands and secondary infection (Danby, Jemec et al. 2013). Abnormalities in keratinocyte antimicrobial peptide production may additionally contribute to defective keratinocyte function and impaired microbial clearance seen with this disease (Bechara, Sand et al. 2012, Dreno, Khammari et al. 2012, Emelianov, Bechara et al. 2012, Hofmann, Saborowski et al. 2012). While antibiotics are widely used to control symptoms in HS, they do not treat the underlying cause of the disease (Yazdanyar and Jemec 2011). Hormonal therapies, including treatment with 5α-reductase inhibitors such as Finasteride reduce disease activity but recurrence of HS is common (Domenech, Matarredona et al. 2012, Randhawa, Hamilton et al. 2013). Traditional disease modifying anti-rheumatic (DMARD) therapies have been largely ineffective in HS. However, targeted biologic therapy including TNF-α inhibitors such as infliximab (Remicade®) (Haslund, Lee et al. 2009, Grant, Gonzalez et al. 2010, Lesage, Adnot-Desanlis et al. 2012, Van Rappard and Mekkes 2012) and adalimumab (Humira®) (Amano, Grant et al. 2010, Miller, Lynggaard et al. 2011, Kimball, Kerdel et al. 2012, van der Zee, Laman et al. 2012, Kimball, Okun et al. 2016) have been used with some success. The U.S. Food and Drug Administration (FDA) recently granted orphan drug designation for the use of adalimumab as an investigational treatment for Hurley stage II and III disease. Other studies have shown that haplotypes of the IL-12Rβ1 impact clinical phenotypes of HS (Giatrakos, Huse et al. 2013). A small study investigating the IL-23/Th17 pathway in HS has demonstrated overexpression of IL-12 and 23 in HS lesional skin and infiltration of HS lesional dermis by IL-17 producing T-helper cells (Schlapbach, Hanni et al. 2011), suggesting that the IL-12/IL-23 pathway may also be a critical driver of this disease. In support of this hypothesis, Ustekinumab (Stelara®), a monoclonal antibody targeting the IL-12/IL-23 common p40 subunit, has been effective in a small number of reported cases (Sharon, Garcia et al. 2012). A retrospective study of surgical patients found lower rates of recurrence and disease progression, as well as longer disease-free interval in patients treated with adjuvant biologic therapy after radical resection for HS (DeFazio, Economides et al. 2015).

The purpose of the current study was to investigate inflammatory cytokines and growth factors in the effluent from HS lesions. The HS effluent was compared to effluent from

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chronic wound specimens because the role of inflammation influencing wound healing in chronic wounds is well-recognized (Loots, Lamme et al. 1998, Eming, Krieg et al. 2007, Li, Chen et al. 2007, Eming, Martin et al. 2014). Wounds that have not healed after more than 3 months of standard local wound care are considered chronic, and these wounds are often arrested in the inflammatory phase of wound healing, thus providing an excellent control group for this study. In differentiating the inflammatory profile of HS lesions compared to chronic wounds, we hope to identify potential local drivers of inflammation unique to HS over and above inflammatory responses seen in patients with chronic wounds, with a view to advancing understanding of the mechanisms and pathogenesis of HS so that novel therapeutic targets can be identified for drug development.

Materials and Methods

This research was conducted through the Wound Etiology and Healing (WE-HEAL) Study, a biospecimen and data repository designed for studying chronic wounds approved by the George Washington University Institutional Review Board (041408). Any patients with an open wound or hidradenitis suppurativa are recruited to the study and give consent for longitudinal data collection and biospecimen collection.

Patients

Wound fluid specimens from 8 patients with HS and 8 age-matched patients with chronic wounds were selected for analysis. Baseline demographics were obtained from the WE-HEAL Study database. The Hidradenitis Suppurativa Score (HSS) (Sartorius, Emtestam et al. 2009, Sartorius, Killasli et al. 2010), a validated hidradenitis disease activity score utilized in clinical trials was used to determine extent of hidradentis activity at the time of specimen collection.

Wound fluid collection

According to standard operating procedures for the WE-HEAL Study, wound effluent specimens were collected using the Levine technique (Angel, Lloyd et al. 2011). This technique has been well validated to ensure standardization throughout all specimens collected in the WE-HEAL Study. After collection, the swabs were immediately placed in 0.65μm pore size centrifugal filters (ultrafree-MC-DV, Merck Millipore, MA, USA). Samples were centrifuged at 12000 rpm for 4 minutes to extract the wound exudate and remove cellular and fibrinous debris. A Barcode Unique Identifier Code (BUIC) system was used to track biospecimens within the WE-HEAL biorepository and ensure that samples can be paired with clinical outcome data without requiring patient identifiers. Samples were stored in -80 °C freezer until analysis. Only samples with >20 μL of wound fluid volume were selected for use in this analysis.

Cytokine measurement by Electrochemiluminescence Assay

Wound fluid contains some heme pigment with can interfere with immune analysis of cytokines by traditional multiplex methods. Thus we elected to utilize the Meso Scale Discovery electrochemiluminescent assay (MSD, Meso Scale Diagnostics, Rockville, MD). This V-Plex system utilizes the principle that electrochemiluminescent labels generate light

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when stimulated by electricity in the appropriate chemical environment (Chowdhury, Williams et al. 2009). The MSD V-Plex cytokine panel 1 and the V-plex proinflammatory panel 1 were used to analyze proinflammatory cytokines in the fluid specimens.

While some wounds are more exudative, to control for variability in volumes, we performed this assay using 10 μL from each sample. Since only swab samples, not wound VAC samples, were used, the variations in wound exudate volume are minimal. Standard volumes of 10μL of wound exudate were utilized for each panel and diluted using the assay diluent according to package insert. For the proinflammatory panel a 10-fold dilution was used, and for cytokine panel-1 a 20-fold dilution was used. All samples were run in duplicate and processed according to the manufacturer instructions.

Statistical analysis

The values for each individual data points were represented as a mean of the replicate wells. Any values above and below the standard fit curve were excluded. Data was analyzed using GraphPad Prism 5.03 (for Windows, GraphPad Software, San Diego California USA). Fishers exact test and Chi-squared tests were used for categorical variables and Student's t-test was used for continuous variables. Results are represented as mean ± SD. A p value less than 0.05 indicates statistical significance; all significance tests were performed and interpreted in a two-sided manner.

Results

Demographics

There was no significant difference in race, sex, presence of diabetes, and cigarette smoking exposures in the HS compared to chronic wound cohorts (Table 1). The mean HSS for the HS cohort was 68.88 (SD ± 41.45) confirming that these patients had moderately active disease.

Pro-inflammatory cytokine profile in HS compared to chronic wound effluent

Comparison of cytokine levels in the effluent from HS specimens compared to those with chronic wounds revealed that levels of interferon-gamma (IFN-γ) were significantly elevated in the HS wound fluid compared to the control subjects with chronic wounds (Table 2, 1418 ± 1501 pg/ml compared to 102.5± 138 pg/ml, p 0.027). HS effluent also had significantly higher levels of TNF-β than chronic wound fluid (Table 2, 9.24 ± 7.22 pg/ml compared to 1.65 ± 2.14 pg/ml, p 0.03). There was no significant difference in any other proinflammatory cytokines including TNF-α, IL-1β, IL-12p70, IL-1α, IL-17A, IL-6, IL-16 and IL-12/IL-23p40.

Anti-inflammatory cytokine profile in HS compared to chronic wound effluent

None of the anti-inflammatory cytokines including IL-10, IL-4, and IL-13 showed differential expression in the HS effluent compared to the chronic wound effluent.

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Proliferation and Growth Factor cytokine profiles in HS compared to chronic wound effluent

The traditional proliferation cytokines, IL-2, IL-15, IL-7 and IL-5 were not significantly different between HS effluent and chronic wound fluid. Similarly, the growth factors GM-CSF and VEGF were not significantly different between the HS and chronic wound effluent.

Discussion

Local molecular drivers of HS are poorly understood. In this study, we were able to show that when compared with effluent from chronic wounds, HS effluent contains statistically significantly higher levels of the cytokines IFN-γ and TNF-β (also known as Lymphotoxin-α, LT-α). This finding supports the hypothesis that IFN-γ may play a crucial role in driving and perpetuating the exuberant inflammation in HS. IFN-γ is a soluble cytokine in the class II interferon family which is predominantly produced by natural killer (NK) cells as part of the early innate immune response and by antigen-stimulated CD-4 cells and CD-8 lymphocytes as an adaptive immune response. IFN-γ is crucial for immunity against intracellular pathogens and plays a role in the host immune response to malignant cells (Schoenborn and Wilson 2007). IFN-γ is a major activator of macrophages and inducer of MHC-I expression, which in turn serves to down regulate IFN-γ production in appropriate circumstances. Aberrant IFN-γ expression is known to be associated with certain autoinflammatory and autoimmune diseases including inflammatory bowel disease (Bouma and Strober 2003) and multiple sclerosis (Neurath, Weigmann et al. 2002).

IFN-γ activates the JAK-STAT pathway, and inhibits the heparan sulfate pathway (Sadir, Forest et al. 1998). It is secreted by T_h1 cells in a positive feedback loop that causes more undifferentiated T_h0 CD4 cells to differentiate into T_h1 cells, while also suppressing T_h2 differentiation (Schoenborn and Wilson 2007). In granuloma development, IFN-γ activates macrophages by blocking phagolysosome maturation. Presentation of antigens to T_h1 helper cells can further stimulate release of IFN-γ resulting in macrophage differentiation into fibroblast-like cells walling off infection (Schroder, Hertzog et al. 2004).

The role of TNF-β/LT-α is less well-characterized. In this study we were able to demonstrate significantly higher levels of TNF-β in the HS compared to the chronic wound patients; however, the absolute levels of TNF-β were modest compared to other cytokines. TNF-β/LT-α physiology is complex. This cytokine is known to play a role in development of lymphoid tissues, lymphoid microenvironment and the development of mucosal associated lymphoid tissue (Iizuka, Chaplin et al. 1999, Gommerman and Browning 2003). Furthermore, TNF-β/LT-α has been implicated in development of ectopic lymphoid structures (Gommerman and Browning 2003). Additionally, recent studies have shown that use of an LT-α specific monoclonal antibody can selectively deplete T_h1 and T_h17 cells ameliorating inflammation in several autoimmune models including collagen-induced arthritis (Chiang, Kolumam et al. 2009), and LT-α has been postulated to play a role clinically in development of rheumatoid arthritis (Calmon-Hamaty, Combe et al. 2011, Calmon-Hamaty, Combe et al. 2011).

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Prior studies investigating cytokine profiles in HS patients have shown high levels of proinflammatory cytokines in pus extracted from HS lesions but low cytokine production in peripheral blood mononuclear cells (PBMC) from patients compared to normal controls (Kanni, Tzanetakou et al. 2015). This suggests that there is compartmentalized cytokine expression in HS. Our findings support this, and in the current study we were also able to compare cytokine profiles in the exudate of HS lesions to those seen in exudate from chronic wounds. By controlling for elevation of cytokines related to the chronicity and persistence of an open wound, we were able to identify cytokines that are likely to be important molecular drivers of inflammation in HS.

IFN-γ and TNF-α act synergistically in mediating the immune response (Ohmori, Schreiber et al. 1997, Vila-del Sol, Punzón et al. 2008), and our findings of marked elevation of IFN-γ and mild elevation of TNF-β are consistent with clinical studies demonstrating response of HS lesions to TNF-α inhibition (Haslund, Lee et al. 2009, Miller, Lynggaard et al. 2011, Kimball, Kerdel et al. 2012, Jemec 2013). The absence of significant TNF-α elevation in this study likely reflects the selection of chronic wounds as a control group. TNF-α is known to be elevated in chronic wounds (Charles, Romanelli et al. 2009, Kirsner 2010, Weinstein and Kirsner 2010) and thus our study did not demonstrate a significant difference in TNF-α concentration in HS exudate compared to chronic wound exudate since both demonstrate high levels of TNF-α. The mild elevation of TNF-β merits further investigation in a larger cohort. Notably, IL-17A was also higher in some of the HS patients but this did not reach statistical significance due to a wide standard deviation in the data. This finding also deserves further investigation in a larger study.

The current study has several limitations that merit discussion. First, the HS subjects studied had a longer lesion duration than the patients with chronic wounds. However, it is well recognized that wounds that have been refractory for more than 3 months are often arrested in the inflammatory phase (Loots, Lamme et al. 1998, Eming, Krieg et al. 2007, Li, Chen et al. 2007, Eming, Martin et al. 2014), and thus this population still provides a valid control group for this study. Additionally, the sample size in this study was small, in part because this was a pilot study designed to be hypothesis generating. The data generated cannot be independently verified on current samples because we do not have sufficient residual wound fluid from these specimens. A larger study is needed to independently verify the findings using both tissue microarray and additional wound fluid cytokine analysis.

In the current study, specimens were collected during routine clinical interventions, rather than targeting patients with specific levels of disease activity. The advantage to this methodology is that in the future we will be able to investigate longitudinal variation in cytokine profiles in response to disease activity and therapeutic interventions. The current study only evaluated the cytokine profile at a single time point, and since distribution of disease activity in our cohort tended to be skewed to patients with more active disease, we are unable to investigate the relationship between cytokine profile and disease activity score with the current data. A body of published literature now supports the role of the immune system in HS and in particular the role of the IL12/23 and Th17 pathways. If trends in cytokine profile with disease activity can be demonstrated, these profiles could be harnessed

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as biomarkers of disease activity to help guide therapeutic interventions for this debilitating disease.

Conclusion

This proof of concept pilot study confirms that cytokine profiles can be reliably measured on HS lesion effluent. IFN- γ was significantly elevated in HS effluent, and likely contributes to the local inflammatory response in HS. TNF-β/LT-α levels were also elevated in HS although the levels were more modest. Further studies are warranted to investigate molecular drivers of tissue injury in HS and the relationship between HS effluent cytokine profile and disease activity since these molecules may have an additional role as biomarkers of disease activity in HS.

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References

Amano M, Grant A, Kerdel FA. A prospective open-label clinical trial of adalimumab for the treatment of hidradenitis suppurativa. Int J Dermatol. 2010; 49(8):950–955. [PubMed: 21128923]

Angel DE, Lloyd P, Carville K, Santamaria N. The clinical efficacy of two semi-quantitative wound-swabbing techniques in identifying the causative organism(s) in infected cutaneous wounds. International Wound Journal. 2011; 8(2):176–185. [PubMed: 21303456]

Bechara FG, Sand M, Skrygan M, Kreuter A, Altmeyer P, Gambichler T. Acne inversa: evaluating antimicrobial peptides and proteins. Ann Dermatol. 2012; 24(4):393–397. [PubMed: 23197903]

Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol. 2003; 3(7):521–533. [PubMed: 12876555]

Calmon-Hamaty F, Combe B, Hahne M, Morel J. Lymphotoxin alpha revisited: general features and implications in rheumatoid arthritis. Arthritis Res Ther. 2011; 13(4):232. [PubMed: 21861866]

Calmon-Hamaty F, Combe B, Hahne M, Morel J. Lymphotoxin alpha stimulates proliferation and pro-inflammatory cytokine secretion of rheumatoid arthritis synovial fibroblasts. Cytokine. 2011; 53(2): 207–214. [PubMed: 21111629]

Charles CA, Romanelli P, Martinez ZB, Ma F, Roberts B, Kirsner RS. Tumor necrosis factor–alfa in nonhealing venous leg ulcers. Journal of the American Academy of Dermatology. 2009; 60(6):951–955. [PubMed: 19344978]

Chiang EY, Kolumam GA, Yu X, Francesco M, Ivelja S, Peng I, Gribling P, Shu J, Lee WP, Refino CJ, Balazs M, Paler-Martinez A, Nguyen A, Young J, Barck KH, Carano RA, Ferrando R, Diehl L, Chatterjea D, Grogan JL. Targeted depletion of lymphotoxin-alpha-expressing TH1 and TH17 cells inhibits autoimmune disease. Nat Med. 2009; 15(7):766–773. [PubMed: 19561618]

Chowdhury F, Williams A, Johnson P. Validation and comparison of two multiplex technologies, Luminex® and Mesoscale Discovery, for human cytokine profiling. Journal of Immunological Methods. 2009; 340(1):55–64. [PubMed: 18983846]

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Cosmatos I, Matcho A, Weinstein R, Montgomery MO, Stang P. Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States. J Am Acad Dermatol. 2013; 69(5):819. [PubMed: 24124817]

Danby FW, Jemec GB, Marsch W, von Laffert M. Preliminary findings suggest hidradenitis suppurativa may be due to defective follicular support. Br J Dermatol. 2013; 168(5):1034–1039. [PubMed: 23320858]

DeFazio MV, Economides JM, King KS, Han KD, Shanmugam VK, Attinger CE, Evans KK. Outcomes After Combined Radical Resection and Targeted Biologic Therapy for the Management of Recalcitrant Hidradenitis Suppurativa. Ann Plast Surg. 2015

Domenech C, Matarredona J, Escribano-Stable JC, Devesa JP, Vicente J, Jaen A. Facial hidradenitis suppurativa in a 28-year-old male responding to finasteride. Dermatology. 2012; 224(4):307–308. [PubMed: 22759836]

Dreno B, Khammari A, Brocard A, Moyse D, Blouin E, Guillet G, Leonard F, Knol AC. Hidradenitis suppurativa: the role of deficient cutaneous innate immunity. Arch Dermatol. 2012; 148(2):182–186. [PubMed: 22004878]

Emelianov VU, Bechara FG, Glaser R, Langan EA, Taungjaruwinai WM, Schroder JM, Meyer KC, Paus R. Immunohistological pointers to a possible role for excessive cathelicidin (LL-37) expression by apocrine sweat glands in the pathogenesis of hidradenitis suppurativa/acne inversa. Br J Dermatol. 2012; 166(5):1023–1034. [PubMed: 22136668]

Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol. 2007; 127:514–525. [PubMed: 17299434]

Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. Science Translational Medicine. 2014; 6(265):265sr266–265sr266.

Esmann S, Dufour DN, Jemec GB. Questionnaire-based diagnosis of hidradenitis suppurativa: specificity, sensitivity and positive predictive value of specific diagnostic questions. Br J Dermatol. 2010; 163(1):102–106. [PubMed: 20331444]

Giatrakos S, Huse K, Kanni T, Tzanetakou V, Kramer M, Grech I, Papadavid E, Katoulis A, Stavrianeas N, Nothnagel M, Platzer M, Bauer M, Giamarellos-Bourboulis EJ. Haplotypes of IL-12Rbeta1 impact on the clinical phenotype of hidradenitis suppurativa. Cytokine. 2013; 62(2): 297–301. [PubMed: 23557799]

Gommerman JL, Browning JL. Lymphotoxin/light, lymphoid microenvironments and autoimmune disease. Nat Rev Immunol. 2003; 3(8):642–655. [PubMed: 12974479]

Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. J Am Acad Dermatol. 2010; 62(2):205–217. [PubMed: 20115947]

Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors. Acta Derm Venereol. 2009; 89(6):595–600. [PubMed: 19997689]

Hessam S, Sand M, Gambichler T, Bechara FG. Correlation of inflammatory serum markers with disease severity in patients with hidradenitis suppurativa (HS). J Am Acad Dermatol. 2015

Hofmann SC, Saborowski V, Lange S, Kern WV, Bruckner-Tuderman L, Rieg S. Expression of innate defense antimicrobial peptides in hidradenitis suppurativa. J Am Acad Dermatol. 2012; 66(6):966–974. [PubMed: 21982063]

Iizuka K, Chaplin DD, Wang Y, Wu Q, Pegg LE, Yokoyama WM, Fu YX. Requirement for membrane lymphotoxin in natural killer cell development. Proc Natl Acad Sci U S A. 1999; 96(11):6336–6340. [PubMed: 10339588]

Jahns AC, Killasli H, Nosek D, Lundskog B, Lenngren A, Muratova Z, Emtestam L, Alexeyev OA. Microbiology of hidradenitis suppurativa (acne inversa) a histological study of 27 patients. APMIS. 2014; 122(9):804–809. [PubMed: 24475943]

Jemec GB. Predicting response to anti-TNF-alpha treatment in Hidradenitis suppurativa. Br J Dermatol. 2013; 168(2):233.

Jemec GBE. Hidradenitis Suppurativa. New England Journal of Medicine. 2012; 366(2):158–164. [PubMed: 22236226]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kanni T, Tzanetakou V, Savva A, Kersten B, Pistiki A, van de Veerdonk FL, Netea MG, van der Meer JW, Giamarellos-Bourboulis EJ. Compartmentalized Cytokine Responses in Hidradenitis Suppurativa. PLoS ONE. 2015; 10(6):e0130522. [PubMed: 26091259]

Kelly G, Sweeney CM, Tobin AM, Kirby B. Hidradenitis suppurativa: the role of immune dysregulation. International Journal of Dermatology. 2014; 53(10):1186–1196. [PubMed: 24961484]

Kimball AB, Kerdel F, Adams D, Mrowietz U, Gelfand JM, Gniadecki R, Prens EP, Schlessinger J, Zouboulis CC, van der Zee HH, Rosenfeld M, Mulani P, Gu Y, Paulson S, Okun M, Jemec GB. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med. 2012; 157(12):846–855. [PubMed: 23247938]

Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, Armstrong AW, Kerdel F, Gold MH, Forman SB, Korman NJ, Giamarellos-Bourboulis EJ, Crowley JJ, Lynde C, Reguiai Z, Prens EP, Alwawi E, Mostafa NM, Pinsky B, Sundaram M, Gu Y, Carlson DM, Jemec GB. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N Engl J Med. 2016; 375(5):422–434. [PubMed: 27518661]

Kirsner R. Biological Agents for Chronic Wounds. American Journal of Clinical Dermatology. 2010; 11(1):23–25. [PubMed: 20586502]

Laffert, Mv, Helmbold, P., Wohlrab, J., Fiedler, E., Stadie, V., Marsch, WC. Hidradenitis suppurativa (acne inversa) early inflammatory events at terminal follicles and at interfollicular epidermis*. Experimental Dermatology. 2010; 19(6):533–537. [PubMed: 19659829]

Lesage C, Adnot-Desanlis L, Perceau G, Bonnet M, Palot JP, Bernard P, Reguiai Z. Efficacy and tolerance of prolonged infliximab treatment of moderate-to-severe forms of hidradenitis suppurativa. Eur J Dermatol. 2012; 22(5):640–644. [PubMed: 22759562]

Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. Clinics in Dermatology. 2007; 25(1): 9–18. [PubMed: 17276196]

Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. J Invest Dermatol. 1998; 111(5):850–857. [PubMed: 9804349]

Miller I, Lynggaard CD, Lophaven S, Zachariae C, Dufour DN, Jemec GB. A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. Br J Dermatol. 2011; 165(2):391–398. [PubMed: 21457202]

Neurath MF, Weigmann B, Finotto S, Glickman J, Nieuwenhuis E, Iijima H, Mizoguchi A, Mizoguchi E, Mudter J, Galle PR, Bhan A, Autschbach F, Sullivan BM, Szabo SJ, Glimcher LH, Blumberg RS. The transcription factor T-bet regulates mucosal T cell activation in experimental colitis and Crohn's disease. J Exp Med. 2002; 195(9):1129–1143. [PubMed: 11994418]

Ohmori Y, Schreiber RD, Hamilton TA. Synergy between Interferon-γ and Tumor Necrosis Factor-α in Transcriptional Activation Is Mediated by Cooperation between Signal Transducer and Activator of Transcription 1 and Nuclear Factor κB. Journal of Biological Chemistry. 1997; 272(23):14899–14907. [PubMed: 9169460]

Randhawa HK, Hamilton J, Pope E. Finasteride for the treatment of hidradenitis suppurativa in children and adolescents. JAMA Dermatol. 2013; 149(6):732–735. [PubMed: 23552442]

Sadir R, Forest E, Lortat-Jacob H. The Heparan Sulfate Binding Sequence of Interferon-γ Increased the On Rate of the Interferon-γ-Interferon-γ Receptor Complex Formation. Journal of Biological Chemistry. 1998; 273(18):10919–10925. [PubMed: 9556569]

Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. British Journal of Dermatology. 2009; 161(4): 831–839. [PubMed: 19438453]

Sartorius K, Killasli H, Heilborn J, Jemec GB, Lapins J, Emtestam L. Interobserver variability of clinical scores in hidradenitis suppurativa is low. Br J Dermatol. 2010; 162(6):1261–1268. [PubMed: 20184581]

Schlapbach C, Hanni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011; 65(4):790–798. [PubMed: 21641076]

Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol. 2007; 96:41–101. [PubMed: 17981204]

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Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-γ: an overview of signals, mechanisms and functions. Journal of Leukocyte Biology. 2004; 75(2):163–189. [PubMed: 14525967]

Sharon VR, Garcia MS, Bagheri S, Goodarzi H, Yang C, Ono Y, Maverakis E. Management of recalcitrant hidradenitis suppurativa with ustekinumab. Acta Derm Venereol. 2012; 92(3):320–321. [PubMed: 22101775]

van der Zee HH, Laman JD, de Ruiter L, Dik WA, Prens EP. Adalimumab (antitumour necrosis factor-alpha) treatment of hidradenitis suppurativa ameliorates skin inflammation: an in situ and ex vivo study. Br J Dermatol. 2012; 166(2):298–305. [PubMed: 22013960]

Van Rappard DC, Mekkes JR. Treatment of severe hidradenitis suppurativa with infliximab in combination with surgical interventions. Br J Dermatol. 2012; 167(1):206–208. [PubMed: 22229974]

Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. J Invest Dermatol. 2013; 133(1):97–103. [PubMed: 22931916]

Vila-del Sol V, Punzón C, Fresno M. IFN-γ-Induced TNF-α Expression Is Regulated by Interferon Regulatory Factors 1 and 8 in Mouse Macrophages. The Journal of Immunology. 2008; 181(7): 4461–4470. [PubMed: 18802049]

Weinstein DA, Kirsner RS. Refractory ulcers: The role of tumor necrosis factor–α. Journal of the American Academy of Dermatology. 2010; 63(1):146–154. [PubMed: 20542177]

Yazdanyar S, Jemec GB. Hidradenitis suppurativa: a review of cause and treatment. Curr Opin Infect Dis. 2011; 24(2):118–123. [PubMed: 21192260]

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Table 1

Baseline demographics of Hidradenitis and Chronic Wound Cohorts.

	HIDRADENITIS SUPPURATIVA (n=8) Mean ± SD	CHRONIC WOUND (n=8) Mean ± SD	P value	
Mean age	41.61 ± 13.81	45.32 ± 10.42	0.55‡	NS
Sex (% female)	50%	50%	1.00 ††	NS
Race (n)	African American: 5 Caucasian: 2 Asian: 1	African American: 3 Caucasian: 5	0.62†	NS
Diabetes mellitus (%)	50%	37.5%	1.00†	NS
Smoking status(n)	Nonsmoker: 5 Current smoker: 2 Past smoker: 1	Nonsmoker: 3 Current smoker: 2 Past smoker: 3	0.47††	NS
HSS score	68.88 ± 41.45			
Hurley Stage				
Stage 1	0			
Stage 2	3			
Stage 3	5			
Wound surface area (cm^2)	n/a	39.69 ± 66.54		
Disease Duration (years, mean ± SD)	9.62 ± 8.45	1.39 ± 0.91	0.02‡	*

‡Students t-test,

†Fisher's exact test,

††Chi square test

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Table 2

Comparison of cytokines profiles from wound fluid in HS and chronic wound patients. IFN-γ and TNF-β are significantly increased in wound fluid from HS patients.

		WOUND FLUID			
		HIDRADENITIS (pg/mL) N=8 Mean ± SD	**CHRONIC WOUND (pg/mL) N=8 Mean ± SD**	**P value**	
	AGE	41.61 ± 13.81	45.32 ± 10.43	0.55	NS
PRO-INFLAMMATORY	INF-γ	1418 ± 1501	102.5 ± 138	0.027	*
	IL-12p70	9.412 ± 7.59	15.02 ± 27.28	0.609	NS
	IL-1β	862.5 ± 1076	1503 ± 3500	0.69	NS
	IL-1α	1126 ± 1746	2549 ± 5565	0.5291	NS
	IL-17A	1006 ± 1652	32.7 ± 37.36	0.12	NS
	IL-6	2377 ± 1604	5451 ± 8180	0.32	NS
	TNF-α	83.26 ± 69.07	65.74 ± 105.4	0.70	NS
	TNF-β	9.24 ± 7.22	1.65 ± 2.14	0.03	*
	IL-16	15277 ± 18785	15586 ± 25553	0.97	NS
	IL12/IL23p40	488.3 ± 570.8	97.86 ± 67.06	0.07	NS
ANTI-INFLAMMATORY	IL-10	19.85 ± 18.74	34.74 ± 69.58	0.57	NS
	IL-4	6.56 ± 4.15	9.77 ± 13.98	0.54	NS
	IL-13	70.98 ± 48.16	55.61 ± 56.10	0.56	NS
PROLIFERATION	IL-2	18.97 ± 18.66	13.16 ± 22.15	0.60	NS
	IL-15	24.5 ± 37.29	5.61 ± 4.75	0.18	NS
	IL-7	22.29 ± 20.49	10.45 ± 6.28	0.14	NS
	IL-5	30.15 ± 33.63	9.314 ± 18.01	0.17	NS
GROWTH FACTOR	GM-CSF	78.45 ± 62.6	82.13 ± 208.8	0.96	NS
	VEGF	632.1 ± 757.4	1544 ± 1765	0.23	NS