Title: Factors associated with treatment satisfaction in patients with hidradenitis suppurativa: results from the Global VOICE project

B. Midgette, BS[1], A. Strunk, MA[1], O. Akilov, MD, PhD[2], A. Alavi, MSc, MD, FRCPC[3], C. Ardon, MD[4], S. Micha, MD[5], F.G. Bechara, MD[6], A.D. Cohen, MD, MPH, PhD[7], S. Cohen, MD, MPH[8], S. Daveluy, MD[9], V. del Marmol[10], M. Delage, MD[11], S. Esmann, MA[12], S. Fisher, RN, MA[13], E.J. Giamarellos-Bourboulis, MD[5], A. Glowaczewska, MD[14], N. Goldfarb, MD[15], E. Gonzalez Brant, MD[2], Ø. Grimstad, MD, PhD[16], S. Guilbault[17], I. Hamzavi, MD[18], R. Hughes, MD, MRCPI[19], J.R. Ingram, DM FRCP[20], G.B.E. Jemec, MD, DMSc[12], Q. Ju, MD[21], N. Kappe, MD[4], B. Kirby, MD, FRCPI[19], J.S. Kirby, MD, MS, Med[22], M.A. Lowes, MD, PhD[23], L. Matusiak, MD, PhD[14], R. Micheletti, MD[24], A.P. Miller[18], D. Moseng, MD[16], H. Naik, MD, MHSc[25], A. Nassif, MD[11], G. Nikolakis, MD[26], S.Y. Paek, MD[27], J.C. Pascual, MD[28], E. Prens, MD, PhD[4], B. Resnik, MD[29], H. Riad, MBBcH, MS, MD[30], C. Sayed, MD[31], S.D. Smith, MBChB, MHL, PhD, FACD[32], Y. Soliman, BA[8], J. Szepietowski, MD, PhD[14], J. Tan, MD, FRCPC[33], L. Thorlacius, MD[12], T. Tzellos, MD, MSc, PhD[16], H. van der Zee, MD, PhD[4], B. Villumsen, M.Sc.Eng[34], L. Wang, MD[21], C. Zouboulis, MD, PhD[26], A. Garg, MD[1]

[1]Department of Dermatology, Donald & Barbara Zucker School of Medicine at Hofstra Northwell, Hempstead, NY

[2]Department of Dermatology, University of Pittsburgh, Pittsburgh, PA, USA

[3]Department of Dermatology, Mayo Clinic Alix School of Medicine, Rochester, MN, USA

[4]Department of Dermatology, Erasmus University Medical Center, Rotterdam, Netherlands

[5]4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece

[6]Department of Dermatology, Venereology and Allergology, St. Josef Hospital, Ruhr-University, Bochum, Germany

[7]Department of Quality Measures and Research , Clalit Health Services, Tel Aviv, Israel

[8]Division of Dermatology, Albert Einstein College of Medicine, Bronx, NY, USA

[9]Department of Dermatology, Wayne State University School of Medicine, Detroit, MI, USA

[10]Department of Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

[11]Department of Dermatology, Institut Pasteur, Centre Medical, Paris, France

[12]Department of Dermatology, Zealand University Hospital, Roskilde, Denmark

[13]Dermatology Department, Emek Medical Center, Afula, Israel

[14]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Poland

[15]Departments of Dermatology, University of Minnesota, Minneapolis, MN, USA

[16]Department of Dermatology, Faculty of Health Sciences, University Hospital of North Norway,

Institute of Clinical Medicine, Arctic University, Tromsø, Norway

[17]Hope For HS, Detroit, MI, USA

[18]Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA

[19]Department of Dermatology, St Vincent's University Hospital, Dublin, Ireland

[20] Division of Infection and Immunity, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, U.K

[21]Department of Dermatology, Renji Hospital School of Medicine, Shanghai Jiaotong University

[22]Department of Dermatology, Penn State Milton S Hershey Medical Center, Hershey, PA, USA

[23]The Rockefeller University, New York City, NY, USA

[24]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[25]Department of Dermatology, University of California, San Francisco, CA, USA

[26]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Centre, Brandenburg Medical School Theodor Fontane, Dessau, Germany

[27]Department of Dermatology, Baylor Scott & White Health, Dallas, TX, USA

[28]Department of Dermatology, Alicante University General Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation), Alicante, Spain

[29]Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, Miami, FL, USA

[30]Dermatology Department, Al Wakra Hospital, Hamad Medical Corporation, Doha, Qatar

[31]Department of Dermatology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

[32]Department of Dermatology, Northern Clinical School, Sydney Medical School, The University of Sydney, Sydney, Australia

[33]Department of Medicine, Western University, Windsor campus, Ontario, Canada

[34]Danish HS Patients' Association, Copenhagen, Denmark

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Corresponding author:
Amit Garg, MD
Donald and Barbara Zucker School of Medicine at Hofstra / Northwell
1991 Marcus Avenue, Suite 300
New Hyde Park, NY, 11042
Email: amgarg@northwell.edu

Reprint requests: Amit Garg

Authors:

Oleg Akilov; akilovoe@upmc.edu

Afsaneh Alavi; alavi.afsaneh@mayo.edu

Christine Ardon; c.ardon@erasmusmc.nl

Styliani Micha ; Stella.Micha94@gmail.com

Falk G. Bechara; f.bechara@klinikum-bochum.de

Arnon D. Cohen; ardcohen@gmail.com

Steven Cohen; srcohen@montefiore.org

Steven Daveluy; sdaveluy@med.wayne.edu

Véronique del Marmol; v.marmol@drvdm.be

Maia Delage; maia.delage-toriel@pasteur.fr

Solveig Esmann; ses@regionsjaelland.dk

Shani Fisher; shani_fi@clalit.org.il

Amit Garg; amgarg@northwell.edu

Evangelos J. Giamarellos-Bourboulis; egiamarel@med.uoa.gr

Amelia Glowaczewska; amelia.glowaczewska@gmail.com

Noah Goldfarb; gold0414@umn.edu

Elena Gonzalez Brant; gonzalezbrantem@upmc.edu

Øystein Grimstad; Oystein.grimstad@unn.no

Sandra Guilbault; sandra@hopeforhs.org

Iltefat Hamzavi; iltefat@hamzavi.com

Rosalind Hughes; r.hughes@svuh.ie

John R. Ingram; ingramjr@cardiff.ac.uk ORCiD 0000-0002-5257-1142

Gregor B. E. Jemec; gbj@regionsjaelland.dk

Qiang Ju; qiangju@aliyun.com

Naomi Kappe; naomi.kappe@gmail.com

Brian Kirby; b.kirby@svuh.ie

Joslyn Kirby; jkirby1@pennstatehealth.psu.edu

Shiv Kirthi; s.kirthi@svuh.ie

Michelle A. Lowes; lowesm8@gmail.com

Lukasz Matusiak; luke71@interia.pl

Robert Micheletti; Robert.micheletti@uphs.upenn.edu

Bria Midgette; bmidgette1@pride.hofstra.edu

Angela Parks Miller; AMILLER5@hfhs.org

Dagfinn Moseng; Dagfinn.moseng@unn.no

Haley Naik; haley.naik@ucsf.edu

Aude Nassif; aude.nassif@pasteur.fr

Georgios Nikolakis; Georgios.nikolakis@klinikum-dessau.de

So Yeon Paek; doctor.paek@gmail.com

Jose Pascual; jcpascualramirez@hotmail.com

Errol Prens; e.prens@erasmusmc.nl

Barry Resnik; bir@drresnik.com

Hassan Riad; hssnrd@yahoo.com

Christopher Sayed; csayed@email.unc.edu

Hanno Segert; m.segert@klinikum-bochum.de

Saxon D. Smith; saxon.smith@sydney.edu.au

Yssra Soliman; yssra.s.soliman@gmail.com

Andrew Strunk; astrunk1@northwell.edu

Jacek Szepietowski; jacek.szepietowski@umed.wroc.pl

Jerry Tan; jerrytan@bellnet.ca

Linnea Thorlacius; lrit@regionsjaelland.dk

Thrasyvoulos Tzellos; thrasyvoulos.tzellos@unn.no

Hessel van der Zee; h.vanderzee@erasmusmc.nl

Bente Villumsen; bente.villumsen@gmail.com

Lanqi Wang; lanqiwang12345@163.com

Christos C. Zouboulis; christos.zouboulis@mhb-fontane.de

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Oleg Akilov

Dr. Akilov has nothing to disclose.

Afsaneh Alavi

Dr. Alavi is investigator for BI and Processa and consultant for Abbvie, BI, Janssen, InflaRx, Novartis and UCB.

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Steven Cohen

Dr. Cohen reports grants from Abbvie Pharmaceuticals, and Honoraria from Verrica Pharmaceuticals

Steven Daveluy

Dr. Daveluy reports personal fees from Abbvie, other from InflaRx

Véronique del Marmol

Dr. del Marmol reports grants from ABBVIE, personal fees from SANOFI

Maia Delage

Dr. Delage has nothing to disclose.

Solveig Esmann

Dr. Esmann has nothing to disclose.

Shani Fisher

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Amit Garg

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Dr. Glowaczewska has nothing to disclose.

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Øystein Grimstad

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Iltefat Hamzavi

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Rosalind Hughes

Dr. Hughes has nothing to disclose.

John R. Ingram

Dr. Ingram reports a stipend as Editor-in-Chief of the British Journal of Dermatology and an authorship honorarium from UpToDate. He is a consultant for Boehringer Ingelheim, ChemoCentryx, Novartis and UCB Pharma and has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio, all in the field of hidradenitis suppurativa (HS). He is co-copyright holder of HiSQOL, Investigator Global Assessment and Patient Global Assessment instruments for HS..

Gregor Jemec

Dr. Jemec reports grants and personal fees from AbbVie, personal fees from Coloplast, personal fees from Pierre Fabre, grants and personal fees from InflaRx, grants and personal fees from Leo Pharma, grants and personal fees from UCB, grants from Janssen-Cilag, grants from Regeneron, grants from Sanofi, grants from Astra Zeneca, other from Miiskin

Qiang Ju

Dr. Ju has nothing to disclose.

Naomi Kappe

Dr. Kappe has nothing to disclose.

Brian Kirby

Dr. Kirby reports grants, personal fees and non-financial support from Abbvie

Joslyn Kirby

Dr. Kirby reports personal fees from AbbVie, personal fees from Incyte, personal fees from ChemoCentryx

Michelle A. Lowes

Dr. Lowes reports personal fees from Abbvie, personal fees from Incyte, personal fees from Xbiotech, personal fees from Janssen

Lukasz Matusiak

Dr. Matusiak reports personal fees from Abbvie, personal fees from Novartis, personal fees from Pierre-Fabre, personal fees from Leo Pharma.

Robert Micheletti

Dr. Micheletti has nothing to disclose.

Bria Midgette

Bria Midgette has nothing to disclose.

Dagfinn Moseng

Dr. Moseng has nothing to disclose.

Haley Naik

Dr. Naik has nothing to disclose.

Aude Nassif

Dr. Nassif has nothing to disclose.

Georgios Nikolakis

Dr. Nikolakis has nothing to disclose.

So Yeon Paek

Dr. Paek has nothing to disclose.

Jose Pascual

Dr. Pascual has nothing to disclose.

Errol Prens

Dr. Prens has nothing to disclose.

Barry Resnik

Dr. Resnik reports personal fees from AbbVie

Hassan Riad

Dr. Riad has nothing to disclose.

Christopher Sayed

Dr. Sayed reports personal fees from Abbvie Inc, personal fees from Novartis, other from InflaRx, other from UCB

Saxon D. Smith

Dr. Smith reports personal fees from ABBVIE, other from ABBVIE, personal fees from ABBVIE

Yssra Soliman

Yssra Soliman has nothing to disclose.

Andrew Strunk

Andrew Strunk has nothing to disclose.

Jacek Szepietowski

Dr. Szepietowski reports personal fees from Abbvie, personal fees from Novartis, personal fees from Pierre-Fabre, personal fees from Menlo Therapeutics, personal fees from Sienna Biopharmaceuticals, personal fees from Leo Pharma, personal fees from Trevi, personal fees from Sandoz, personal fees from Sanofi Genzyme, personal fees from Janssen-Cilag, personal fees from Amgen, personal fees from Galapagos, personal fees from InflaRx, personal fees from Regeneron, personal fees from UCB.

Jerry Tan

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Linnea Thorlacius

Dr. Thorlacius has nothing to disclose.

Thrasyvoulos Tzellos

Dr. Tzellos reports grants and personal fees from Abbvie, grants and personal fees from UCB

Hessel van der Zee

Dr. van der Zee reports personal fees from ABBVIE, personal fees from INFLARX, personal fees from NOVARTIS, personal fees from GALDERMA

Bente Villumsen

Dr. Villumsen has nothing to disclose.

Lanqi Wang

Dr. Wang has nothing to disclose.

Christos Zouboulis

Dr. Zouboulis reports personal fees from AbbVie, personal fees from AbbVie, grants from AbbVie, personal fees from Idorsia, personal fees from Inflarx, grants from Inflarx, personal fees from Novartis, grants from Novartis, personal fees from UCB, grants from UCB, other from Incyte

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Abbreviations:
HS: hidradenitis suppurativa
OR: odds ratio
CI: confidence interval
BMI: body mass index (calculated as weight in kilograms divided by height in meters squared)
VOICE: survey of impact and healthcare needs
IV: intravenous
IQR: interquartile range
TNF: tumor necrosis factor
IL: interleukin

What's already known about this topic?

- Nearly half of patients with hidradenitis suppurativa report dissatisfaction with treatments.

What does this study add?

- Satisfaction with treatment is increased by receiving care from a dermatologist and treatment with biologics

  Satisfaction with treatment is decreased by accumulation of comorbid conditions including depression, as well as higher flare frequency.

Summary

Background: Nearly half of patients with hidradenitis suppurativa report dissatisfaction with treatment. However, factors related to treatment satisfaction have not been explored.

Objectives: The purpose of this study was to measure association between treatment satisfaction and clinical and treatment-related characteristics among patients with HS.

Methods: Treatment satisfaction was evaluated utilizing data from a cross-sectional global survey of HS patients recruited from 27 institutions, mainly HS referral centers, in 14 different countries from October 2017 through July 2018. Primary outcome was patients' self-reported overall satisfaction with their current treatments for HS, rated on a 5-point scale from "very dissatisfied" to "very satisfied".

Results: The final analysis cohort comprised 1,418 HS patients, most of whom were European (55%, 780/1418) or North American (38%, 542/1418), and female (85%, 1210/1418). Overall, 45% (640/1418) of participants were either dissatisfied or very dissatisfied with their current medical treatment. In adjusted analysis, patients primarily treated by a dermatologist for HS had 1.99 (95% CI 1.62-2.44; p<.001) times the odds of being satisfied with current treatment than participants not primarily treated by a dermatologist. Treatment with biologics was associated with higher satisfaction (OR 2.36; 95% CI 1.74-3.19; p<.001) relative to treatment with non-biologic systemic medications. Factors associated with lower treatment satisfaction included smoking (OR 0.78, 95% CI 0.62-0.99; active vs. never), depression (OR 0.69, 95% CI 0.54-0.87), increasing number of comorbidities (OR 0.88 per comorbidity; 95% CI 0.81-0.96), and increasing flare frequency.

Conclusions: There are several factors which appear to influence satisfaction with treatment among HS patients, including treatment by a dermatologist, treatment with a biologic medication, and accumulation of comorbid conditions, including depression, and flare frequency. Awareness of these factors may support partnered decision making with the goal of improving treatment outcomes.

Introduction

The objective of the Global Survey Of Impact and Healthcare Needs (Global VOICE) project was to evaluate unmet needs in HS from the perspective of patients with the goal of supporting awareness initiatives in public and medical sectors, multidisciplinary approaches to care, advances in treatment, development of the research agenda, as well advocacy and philanthropy efforts. In the primary analysis, HS patients described a mean delay in diagnosis of 10 years.[1] Patients experienced flare daily, weekly, or monthly in 23%, 30%, and 31%, respectively.[1] Approximately 60% rated recent HS-related pain as moderate or higher, while nearly 5% described recent pain to be worst possible.[1] Patients reported frequent visits to the emergency department and hospital for their symptoms.[1] An extreme impact on life was reported by over 40% of patients, and nearly 15% were disabled due to disease.[1] Overall, nearly 50% of HS patients were dissatisfied with their medical treatments.[1]

Treatment in HS remains the most fundamentally important gap in care for the disease state.[1] To date, there is one regulatory approved treatment for moderate to severe HS, wherein about half of patients are expected to have an approximate 50% improvement from baseline in count of inflammatory nodules and abscesses.[2] Information from HS patients on factors influencing satisfaction with treatment may support patient centered strategies to optimize outcomes. The purpose of this study was to measure the association between treatment satisfaction and clinical and treatment-related characteristics among patients with HS.

Materials and Methods

Study Population and Eligibility Criteria

We assessed treatment satisfaction utilizing data from a cross-sectional global survey of patients with HS. The questionnaire was administered to 27 institutions, mainly HS referral centers, in 14 different countries from October 2017 through July 2018. Participants were provided with a separate web link to the survey depending on their language. Patients were eligible for inclusion in the analysis if they self-

reported being diagnosed with HS by a licensed healthcare provider, and if they were not missing data for the study outcome or covariates.

Data Collection

The questionnaire was comprised of 50 questions related to patient demographics, perspectives on diagnosis and care, pain and symptoms, life impact, comorbid conditions, and treatment. The primary outcome was patients' self-reported overall satisfaction with their current treatments for HS, rated on a 5-point scale from "very dissatisfied" (1) to "very satisfied" (5). Associations between treatment satisfaction and the following predictor variables were explored: BMI, tobacco use (current, former, never), primary management of HS by a dermatologist (yes/no), depression, anxiety, number of comorbidities, treatment type, and flare frequency. BMI was calculated from self-reported height and weight and categorized as underweight/normal weight (<25.0), overweight (25.0-29.99), obese class 1 (30.0-34.99), obese class 2 (35.0-39.99), and obese class 3 ($\geq$ 40.0). Participants reported whether they had been diagnosed with any of the following comorbidities: acne; excessive use or addition to alcohol, other substances, or medications; anxiety; spondyloarthritis; coronary artery disease; Crohn's disease; depression; diabetes mellitus (Type 2, adult onset); hypertension; infertility; myocardial infarction; polycystic ovarian syndrome; pyoderma gangrenosum; raised cholesterol; sexual dysfunction; ulcerative colitis. When analyzing relationships with treatment satisfaction, anxiety and depression were treated as separate binary variables, and the remaining comorbidities were summarized in a continuous count variable. Current treatment type was classified as topical or injection only, non-biologic systemic, biologic, or no medical treatment. Non-biologic systemics included medications such as oral and IV antibiotics, oral anti-androgens, oral retinoids, dapsone, oral corticosteroids, among others. Biologics included medications such as adalimumab, infliximab, etanercept, anakinra, ixecizumab, secukinumab, and ustekinumab. Topical or injection medications included topical antibiotics, topical and injectable corticosteroids, anti-bacterial/ anti-septic washes, and similar treatments. Patients reporting use of medications concurrent in multiple treatment categories (e.g., biologic and non-biologic systemic, or non-biologic systemic and

topical) were grouped according to the following hierarchy: 1) biologic; 2) non-biologic systemic; 3) topical. Accordingly, treatment groups were mutually exclusive.

Statistical Analysis

Demographic and clinical characteristics are provided for the overall eligible sample using the median and IQR for quantitative variables, and using counts and percentages for categorical variables. The percentage of patients reporting each level of treatment satisfaction (ranging from "very dissatisfied" to "very satisfied"), was calculated for the overall sample and for subgroups according to the predictor variables described above. A partial proportional odds model (i.e. ordinal logistic regression) was used to assess the association between treatment satisfaction and each predictor variable while adjusting for all other covariates. The proportional odds assumption for a given covariate implies that the odds ratios based on different cut points for an ordinal outcome do not vary. The present analysis allowed for non-proportional odds for the comparison of no treatment to the non-biologic systemic reference group due to a violation of this assumption.

Results

A total of 1,927 participants completed the survey. Among them, 99 participants were excluded from the analysis due to a response of "no" to the question, "Have you been diagnosed with hidradenitis suppurativa by a licensed health care provider?" There were 410 participants who were excluded with missing data for at least one variable of interest, which resulted in a final analysis population of 1,418.

The demographic and clinical characteristics of eligible patients are described in **Table 1**. Most participants were from Europe (55%, 780/1418) or North America (38%, 542/1418), and were female (85%, 1210/1418). A majority of participants were either being treated with a non-biologic systemic medication (42%, 519/1418) or receiving no medical treatment at all (32%, 451/1418). Fewer participants reported being treated with a biologic (14%, 195/1418) or topical/injectable medication only (13%, 181/1418). In 62% of cases, participants had at least 1 comorbidity, including depression (36%, 511/1418) and anxiety (37%, 518/1418).

Table 2 describes treatment satisfaction stratified by patient characteristics. Overall, 45% (640/1418) of participants were either dissatisfied or very dissatisfied with their current medical treatment. In bivariable analysis, men were more likely to be satisfied or very satisfied with their treatment compared to women (38% vs. 28%, respectively). Among the 195 participants currently treated with a biologic, 51% (100/195) were satisfied or very satisfied with their treatment. Of those reporting no current medical treatment, 22% (98/451) were satisfied or very satisfied, and 51% (228/451) were dissatisfied or very dissatisfied. Participants whose HS was primarily managed by a dermatologist were more likely to be satisfied or very satisfied with their treatment (36%, 311/856), compared to participants who had a non-dermatologist as their main treating physician [19% (107/562) satisfied or very satisfied]. As few as 23% (119/511) of participants who were diagnosed with depression were either satisfied or very satisfied with their current HS treatment. Regarding smoking status, 26% (160/624) of active smokers, 31% (117/379) of former smokers, and 34% (141/415) of never smokers were satisfied or very satisfied with their current HS treatment.

Adjusted results of the partial proportional odds regression model for treatment satisfaction are provided in **Table 3**. In adjusted analysis, participants primarily treated by a dermatologist for HS had 1.99 (95% CI 1.62-2.44; p<.001) times the odds of being more satisfied with their current treatment than participants not primarily treated by a dermatologist. Treatment with biologics was associated with higher satisfaction (OR 2.36; 95% CI 1.74-3.19; p<.001) relative to treatment with non-biologic systemic medications. Tobacco smoking (OR 0.78, 95% CI 0.62-0.99; active vs. never), depression (OR 0.69, 95% CI 0.54-0.87), increasing number of comorbidities (OR 0.88 per comorbidity; 95% CI 0.81-0.96), and increasing flare frequency were associated with lower satisfaction.

Discussion

In this Global VOICE analysis, a high proportion of HS patients described dissatisfaction with treatment. The greatest likelihood for satisfaction with treatment was when care for HS was primarily provided by a dermatologist and when treatment was with a biologic medication. Lower likelihood of

treatment satisfaction was observed among active tobacco smokers, those with increasing number of comorbidities, and those with depression. Increasing flare frequency was also associated with lower degrees of treatment satisfaction. Delay in diagnosis and BMI status were not significantly associated with satisfaction with treatment in adjusted analysis.

Slightly more than half of participants in this study were primarily being managed by a dermatologist for their HS. This percentage is lower than we expected, given that patients were enrolled from HS referral centers largely in the US and Europe. In a separate analysis among over 40,000 HS patients in the US, only approximately 20% had an encounter with a dermatologist.[3] Taken together, these results may imply low awareness around the role of dermatologists in the care of HS patients, as well as highlight the difficulty in accessing dermatologists. Indeed 37% of participants in the Global VOICE study previously reported that access to dermatologists was difficult.[1] Improving awareness and access may be critical to improving outcomes for HS patients, as it has been previously showing that care by a dermatologist offers higher likelihood of treatment initiation and treatment escalation.[4]

There was a low percentage of participants currently receiving a biologic medication. In a previous cohort study including over 25,000 HS patients in the US, less than 2% of patients had received a prescription for a tumor necrosis factor (TNF) inhibitor.[5] While no treatment is considered to be uniformly effective, or without side effect, in HS, targeted therapies including TNF,[2,6,7] and interleukin (IL)-17 inhibitors have shown the greatest efficacy among HS treatments with the additional secondary outcomes of reduced pain and flare frequency and improved quality of life.[2,8,9] Patients in this analysis also had higher likelihood of treatment satisfaction with use of biologic therapy. Supporting satisfactory outcomes for HS patients will necessitate the collective effort of medical, industry, regulatory, payor and advocacy sectors engaged in the disease state to develop safe and highly efficacious treatments, to provide access to these treatments, to administer and monitor these medications, and importantly to earn the trust of patients, who are already have a few vulnerabilities related to having HS, in prescribing these medications.

Tobacco smoking appears to be a risk factor for developing disease,[10] and HS patients who smoke may have more severe disease.[4,11,12] Active smokers in this analysis experienced a lower likelihood of treatment satisfaction. Lower treatment satisfaction may be related to more active disease in the context of tobacco smoking, or perhaps a mitigation of response to therapy among smokers. While the advantages of smoking cessation to disease activity or response to therapy in HS have not yet been established, there is clear benefit to overall health status with smoking cessation as well as reduction, both of which should be encouraged.

Hidradenitis suppurativa is associated with a high comorbidity burden,[13,14] which includes depression.[15] While directionality and putative mechanisms linking HS to comorbidities is yet to be established, it is possible that higher inflammatory disease burden in HS results in accumulation of comorbid conditions. As such, comorbidities may also reflect more severe disease and consequently lower likelihood of satisfaction with treatment. Comorbid conditions, including depression, also pose significant life impact for patients which may also influence perception of treatment satisfaction. Comorbidity screening and early management in HS may reduce mortality,[16] improve quality of life, and improve treatment satisfaction. Dermatologists familiar with evidence-based comorbidity screening guidelines will be in the best position to support and advocate for comprehensive care strategies for HS patients.[14]

It is likely that even patients with adequate response to treatments will experience flare related to the natural course of disease. However, high frequency of flares reflects poor disease control and results in symptoms of increased pain and drainage. Patients with flares also seek acute care in emergency departments and hospitals,[1,17] which is not likely necessary for appropriate acute management. In the absence of remitting therapies, utilizing treatments which reduce flare frequency and duration,[9] and improving urgent access to dermatologists for the most appropriate interventions may augment satisfaction with treatment.

There are several limitations in this study. We relied on self-reported data which could have resulted in inaccuracies. Participants with missing data were excluded from the study which limited the amount of data for analysis. The participants in our study were enrolled from HS referral clinics, and thus the sample may reflect the experiences of patients with more severe disease. We did not collect measures of HS severity. Accordingly, comparisons of satisfaction across treatment groups may be confounded by disease severity, which is related to treatment indication. However, the expected direction of this bias would be in favor of non-biologic systemics or topicals, which are indicated for less severe disease. The increased satisfaction among patients treated with biologics despite potentially worse disease severity thus provides stronger evidence for satisfaction with these treatments. We additionally attempted to account for confounding by disease severity by controlling for flare frequency in the ordinal logistic regression model.

In conclusion, number of factors appear to influence satisfaction with treatment among HS patients, including treatment by a dermatologist, treatment with a biologic medication, accumulation of comorbid conditions, including depression, and flare frequency. Awareness of these factors by physicians and patients may support joined decision making which may improve patients ‘outcomes.

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Table 1. Descriptive statistics for patients with HS

Characteristic	**Overall (N=1,418)**
Continent	
Europe	780 (55)
North America	542 (38)
Asia	33 (2.3)
Australia	27 (1.9)
Africa	24 (1.7)
South America	12 (0.8)
Age (yrs.), n (%)	
18-30	419 (30)
31-40	463 (33)
41-50	334 (24)
51-60	164 (12)
61 +	38 (2.7)
Sex, n (%)	
Female	1210 (85)
Male	208 (15)
BMI category, n (%)	
Underweight/Normal weight (<25.0)	294 (21)
Overweight (25.0-29.99)	334 (24)
Obese 1 (30.0-34.99)	341 (24)
Obese 2 (35.0-39.99)	205 (15)
Obese 3 ($\geq$ 40.0)	244 (17)
Smoking status, n (%)	
Never smoker	415 (29)
Active smoker	624 (44)
Former smoker	379 (27)
Treatment type	
Non-biologic systemic	519 (42)
Biologic	195 (14)
Topical or injection only	181 (13)

No current medical treatment	451 (32)
Delay in Diagnosis (yrs.), Median (IQR)	8 (3, 15)
Main physician for HS is a dermatologist, n (%)	
No	562 (40)
Yes	856 (60)
Depression, n (%)	
No	907 (64)
Yes	511 (36)
Anxiety, n (%)	
No	900 (64)
Yes	518 (37)
Comorbidity count	
Median (IQR)	1 (0, 2)
Median [Min, Max]	1 [0, 7]
0 (categorical)	540 (38)
1 (categorical)	485 (34)
2 (categorical)	248 (17)
3 or more (categorical)	145 (10)
Flare frequency, n (%)	
Every 6 months	89 (6.3)
Every 3 months	135 (9.5)
Monthly	437 (31)
Weekly	424 (30)
Daily	333 (24)

Table 2. Treatment satisfaction stratified by patient characteristics

Subgroup	Very Satisfied %	Satisfied %	Neutral %	Dissatisfied %	Very Dissatisfied %
Overall	11	19	25	27	18
Age (yrs.)					
18-30 (n=419)	6.9	18	23	30	22
31-40 (n=463)	8.0	17	27	29	18
41-50 (n=334)	16	20	24	25	14
51-60 (n=164)	16	20	27	20	16
61 + (n=38)	16	21	32	21	11
Sex					
Male (n=208)	14	24	30	20	12
Female (n=1210)	10	18	25	28	19
BMI category, n (%)					
Underweight/Normal weight [<25.0] (n=294)	13	22	20	29	16
Overweight [25.0-29.99] (n=334)	13	18	28	26	15
Obese 1 [30.0-34.99] (n=341)	11	19	27	26	18
Obese 2 [35.0-39.99] (n=205)	9.8	16	27	27	20
Obese 3 [≥ 40.0] (n=244)	6.6	17	25	28	23
Smoking status					
Never smoker (n=415)	11	23	25	27	14
Former smoker (n=379)	12	19	27	24	18
Active smoker (n=624)	10	15	25	29	21
Treatment type					
Non-biologic systemic (n=519)	8.6	19	24	34	15
Biologics (n=195)	17	34	22	17	9.7
Topical or injection only (n=181)	13	19	28	26	13
No medical treatment (n=451)	10	12	28	23	28
Main physician for HS is a dermatologist					
Yes (n= 856)	13	23	25	27	12
No (n=562)	7.8	11	26	28	27
Depression diagnosis					
Yes (n=511)	8.2	15	21	30	26
No (n=907)	12	21	28	26	14
Anxiety diagnosis					
Yes (n=518)	7.3	15	22	35	21
No (n=900)	13	21	27	23	16

Flare frequency					
Every 6 months (n=89)	30	26	22	12	9.0
Every 3 months (n=135)	20	28	33	13	6.7
Monthly (n=437)	11	25	26	26	12
Weekly (n=424)	6.6	13	25	34	22
Daily (n=333)	6.6	12	23	30	29

Table 3. Factors associated with treatment satisfaction among patients with HS

Variable	Adjusted OR[a,b] (95% CI)	p-value
Delay in diagnosis (per 1-yr.)	1.00 (0.99-1.01)	0.66
Comorbidity count (per 1-unit increase)	0.88 (0.81-0.96)	0.006
Age (yrs.)		
18-30	Ref.	Ref.
31-40	1.17 (0.91-1.50)	0.22
41-50	1.84 (1.38-2.46)	<0.001
51-60	1.60 (1.11-2.31)	0.01
61 +	1.57 (0.84-2.93)	0.16
Sex, male vs. female (ref.)	1.22 (0.92-1.61)	0.17
BMI category, n (%)		
Underweight/Normal weight	Ref.	Ref.
Overweight	1.20 (0.90-1.59)	0.22
Obese 1	1.11 (0.83-1.47)	0.48
Obese 2	1.01 (0.72-1.40)	0.97
Obese 3	1.10 (0.79-1.52)	0.55
Smoking status		
Never smoker	Ref.	Ref.
Former smoker	0.82 (0.63-1.07)	0.14
Active smoker	0.78 (0.62-0.99)	0.04
Treatment type		
Non-biologic systemic	Ref.	Ref.
Biologics	2.36 (1.74-3.19)	<0.001
Topical or injection only	1.06 (0.78-1.44)	0.71
Main physician for HS is a dermatologist, Yes vs. No (ref.)	1.99 (1.62-2.44)	<0.001
Depression diagnosis, Yes vs. No (ref.)	0.69 (0.54-0.87)	0.002
Anxiety diagnosis, Yes vs. No (ref.)	0.92 (0.73-1.17)	0.51
Flare frequency		
Every 6 months	Ref.	Ref.
Every 3 months	0.83 (0.51-1.35)	0.44
Monthly	0.43 (0.28-0.66)	<0.001
Weekly	0.23(0.15-0.35)	<0.001
Daily	0.18 (0.11-0.28)	<0.001
OR for No medical treatment vs. non-biologic systemic (ref)[c]		
Y $\geq$ 5	1.29 (0.87-1.93)	.20
Y $\geq$ 4	0.74 (0.55-1.00)	.05
Y $\geq$ 3	0.97 (0.75-1.26)	.84
Y $\geq$ 2	0.50 (0.37-0.67)	<.001

a – Adjusted odds ratios are based on a partial proportional odds model including terms for all of the covariates in the table above, as well terms allowing for nonproportional odds for the comparison of no medical treatment and non-biologic systemic (ref.)

b – Odds ratio > 1 signifies higher odds of greater treatment satisfaction compared to the reference group

c – Odds ratios are reported separately for each cutpoint of the treatment satisfaction outcome (Y=1=Very dissatisfied through Y=5=Very Satisfied) due to violation of the proportional odds assumption.