PROFESSOR ANGELO VALERIO MARZANO (Orcid ID : 0000-0002-8160-4169)
DR GIOVANNI GENOVESE (Orcid ID : 0000-0002-7636-958X)
PROFESSOR PAOLO GISONDI (Orcid ID : 0000-0002-1777-9001)
PROFESSOR ANNALISA PATRIZI (Orcid ID : 0000-0002-8398-0483)
DR LUCA FANIA (Orcid ID : 0000-0003-4194-932X)
DR FRANCESCA PRIGNANO (Orcid ID : 0000-0002-5997-2045)
DR LAURA ATZORI (Orcid ID : 0000-0002-8105-1402)
PROFESSOR MARINA VENTURINI (Orcid ID : 0000-0001-6800-3695)

Article type : Original Article

Evidence for a “window of opportunity” in hidradenitis suppurativa treated with adalimumab: a retrospective, real-life multicenter cohort study

A.V. Marzano,[1,2,*] G. Genovese,[1,2] G. Casazza,[3] C. Moltrasio,[1,2] P. Dapavo,[4] G. Micali,[5] R. Sirna,[6] P. Gisondi,[7] A. Patrizi,[8] V. Dini,[9] D. Bianchini,[10] L. Bianchi,[11] L. Fania,[12] F. Prignano,[13] A. Offidani,[14] L. Atzori,[15] V. Bettoli,[16] S.P. Cannavò,[17] M. Venturini,[18] M. R. Bongiorno,[19] A. Costanzo,[20] G. Fabbrocini[21§] and K. Peris[22§]

1) Dermatology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
2) Department of Physiopathology and Transplantation, Università degli Studi di Milano, Milan, Italy
3) Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Università degli Studi di Milano, Milan, Italy.
4) Department of Medical Sciences, University of Turin, Turin, Italy
5) Dermatology Clinic, University of Catania, Catania, Italy.
6) Dermatology Unit, Department of Surgery, Misericordia Hospital, Grosseto, Italy
7) Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy
8) Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
9) Department of Dermatology, University of Pisa, Pisa, Italy
10) Dermatologic Clinic, Department of Internal Medicine and Medical Specialties, “La Sapienza” University, Rome, Italy
11) Department of Dermatology, University of Rome “Tor Vergata”, Rome, Italy

12) First Dermatology Clinic and Clinical Epidemiology Unit, Istituto Dermopatico dell'Immacolata, IDI-IRCCS, Rome, Italy
13) Department Health Science Section of Dermatology, University of Florence, Florence, Italy
14) Dermatological Clinic Department of Clinical and Molecular Sciences, Polytechnic University of the Marche Region, Ancona, Italy
15) Unit of Dermatology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
16) Department of Medical Sciences, Section of Dermatology, University of Ferrara, Ferrara, Italy
17) Department of Clinical and Experimental Medicine, Section of Dermatology, University of Messina, Messina, Italy.
18) Department of Dermatology, ASST Spedali Civili di Brescia, Brescia, Italy
19) Section of Dermatology, Department of Health Promotion, Maternal-Infant, Internal Medicine and Specialization, University of Palermo, Italy
20) Dermatology Unit, IRCCS Humanitas Clinical and Research Center, Rozzano (Milan), Italy
21) Department of Dermatology, University of Naples Federico II, Italy
22) Institute of Dermatology, Università Cattolica – Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[*] **Corresponding author**:
Angelo Valerio Marzano; angelo.marzano@unimi.it

[§]Gabriella Fabbrocini and Ketty Peris contributed equally to this article

Manuscript word count: 2566
Table count: 3
Figure count: 1

Funding sources: none

Conflicts of interest: none

CAPSULE SUMMARY

What's already known about this topic?

- Adalimumab is an effective and safe biologic licenced for the treatment of moderate-to-severe hidradenitis suppurativa (HS) after failure of conventional treatments
- There are not reliable parameters that predict the clinical response to adalimumab in this disease

What does this study add?

- The "therapeutic delay", defined as the time from HS onset to adalimumab initiation, significantly correlated to lack of clinical response to this drug , particularly at week 16 of treatment
- This study suggests that using adalimumab in early phases of HS should be highly encouraged

ABSTRACT

Background: The anti-tumour necrosis factor (TNF)-α adalimumab is the only licenced biologic for moderate-to-severe hidradenitis suppurativa (HS). No predictors of response have been identified so far.

Objective: To identify clinical parameters predicting response to adalimumab and confirm its efficacy/ safety.

Methods: Data of 389 HS patients treated with adalimumab in 21 Italian centres were reviewed. Sex, ages at onset/diagnosis/baseline, body mass index, smoking, phenotypes, previous treatments, concomitant antibiotics , and "therapeutic delay", defined as the time from HS onset to adalimumab initiation, were assessed. Response to adalimumab and its impact on quality of life (QoL) were evaluated using "Hidradenitis Suppurativa Clinical Response" (HiSCR) and "Dermatology Life Quality Index" (DLQI)/"Visual Analogue Scale for pain" (VAS pain), respectively. Logistic regression analysis was performed.

Results: The "therapeutic delay" correlated to lack of response to adalimumab at week 16 (OR,1.92 for therapeutic delay ≥ 10 years; 95% CI,1.28-2.89; P=0.0016). HiSCR was achieved in 43.7% and 53.9% patients at week 16 and 52, respectively. Significant reductions in both DLQI and VAS pain were found between week 16 *versus* baseline (p<0.0001 for both) and week 52 *versus* baseline (p<0.0001 for both). Previous immunosuppressants inversely correlated to HiSCR at week 52 [OR=1.74, 95% CI 1.04-2.91, p=0.0342].

Conclusion: Inverse correlation between therapeutic delay and clinical response was found, supporting early adalimumab use and providing evidence for a "window of opportunity" in HS. Adalimumab efficacy and safety were confirmed, along with patients' QoL improvement**. I**mmunosuppressants could negatively influence response to adalimumab inducing a switch to non-TNFα -driven pathways.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory systemic disease affecting the skin with nodules, abscesses and fistulas on the axillary, inguinal and breast folds and on anogenital areas.[1,2] Disease severity ranges from mild HS presenting with localized lesions to severe HS manifesting as multiple areas of inflammation, nodules and abscesses possibly forming plaques and interconnected sinus tracts, leading to hypertrophic scars.[3] The prevalence of disease is around 1% in Western Europe,[1,4] and, of note, the average interval from the self-reported onset of symptoms to diagnosis is 7.2 years.[5] HS is a debilitating disease interfering with many activities of daily life. A recent study demonstrated that HS may have a greater impact on quality of life compared to psoriasis and other chronic medical conditions.[6]

The HS pathogenesis is complex and not completely elucidated but an innate immunity dysfunction leading to autoinflammation has recently been reported to play a crucial role,[7,8] with overexpression of proinflammatory cytokines such as interleukin (IL)-1β, IL-17, and tumour necrosis factor (TNF)-α both in the lesional skin and in the serum of patients.[9-12] Adalimumab (Humira®), a fully human IgG monoclonal antibody against TNF-α is currently the only approved drug to treat moderate-to-severe HS based on the 12-week, placebo-controlled periods of the two, phase-3 PIONEER trials.[13] Adalimumab at weekly dose of 40 mg is an effective and safe therapeutic option also for long-term control of moderate-to-severe HS.[14,15] We conducted a real-life multicenter study to assess the impact of different clinical parameters on clinical response to adalimumab in a large cohort of moderate-to-severe HS patients at week 16 and week 52 after adalimumab initiation.

METHODS

Demographics

In this real-life retrospective multicenter study, 21 Italian Dermatology Units contributed to collect demographic and clinical data of patients with moderate-to-severe HS undergoing adalimumab treatment from January 2016 to December 2018. Data included sex, age at HS onset (≤30; 30-50; >50 years), age at diagnosis (≤29; >29 years), age at adalimumab initiation (≤30; 30-50; <50 years), body mass index [BMI] (≤25; 25-30; >30 kg/m2), smoking (never smokers, current smokers, ex-smokers), family history of HS, comorbidities, treatments prior to and concomitant with adalimumab, and HS phenotypes according to the Van der Zee & Jemec classification.[16] The latter one distinguishes six different clinical presentations, namely the regular, frictional furuncle, scarring folliculitis, conglobata, syndromic and ectopic type.[16] The "therapeutic delay" was assessed as the time, in years, from HS onset to adalimumab initiation.

To be part of this study, each centre was asked to provide data of patients aged ≥ 18 years, affected with moderate-to-severe HS defined as having at baseline either Hurley stage ≥ 2 and International Hidradenitis Suppurativa Severity Score System (IHS4)[17] ≥ 4.

According to the Italian Drug Agency (AIFA) recommendations, only patients resistant to standard first-line treatments, such as systemic antibiotics including tetracyclines (doxycycline and minocycline), clindamycin plus rifampicin and/or acitretin can be treated with adalimumab. We also evaluated whether patients had been given previous off-label systemic treatments, including immunosuppressive (cyclosporine, corticosteroids) and immunomodulating (dapsone, zinc gluconate) agents or retinoids other than acitretin, namely isotretinoin.

Patients were treated with adalimumab 160 mg on day 1, 80 mg on day 15 and a single 40 mg injection from week 4 onwards. Patients were assessed for their clinical response at week 16 and at week 52 after initiation of adalimumab treatment. All patients agreed with the treatment regimen and signed a written consent form to use personal data for the present study. In view of the retrospective nature of the study, only a notification to the Ethical Committee of the principal investigator Center (IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) was requested.

Disease severity, quality of life and clinical response to adalimumab

At baseline, the patients were stratified according to Hurley stage,[3] a classification system subdivided in stage 1 (single or multiple abscesses without sinus tract formation or scarring), stage 2 (recurrent abscesses with one or more sinus tracts and scarring widely separated by normal skin) and stage 3 (diffuse involvement with multiple sinus tracts and no intervening normal skin). Disease severity was determined using IHS4[17] at baseline, week 16 and week 52. It is a recently validated scoring system calculated by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4), with a total score of ≤ 3 defining mild, 4-10 defining moderate and ≥ 11 defining severe disease.

The Dermatology Life Quality Index (DLQI) questionnaire[18] and the Visual Analogue Scale for pain (VAS pain),[19] which are measurement instruments widely accepted to evaluate quality of life (QoL) in HS, were also collected at baseline, week 16 and week 52.

Response to adalimumab was measured at week 16 and at week 52 by means of Hidradenitis Suppurativa Clinical Response (HiSCR).[20] Based on this efficacy variable, clinical response is defined as an at least 50% reduction in total inflammatory nodule and abscess count (AN count), with no increase in abscess and/or draining fistula count relative to baseline. No response is defined as less than 50% reduction in total AN count or increase in abscess or draining fistula count relative to baseline.

Statistical analysis

Continuous variables are reported as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. Categorical data are reported as counts (percentages). A logistic regression analysis was performed to assess some patients' characteristics as predictors of non-response. The two endpoints considered were response to adalimumab at week 16 and at week 52. The following predefined patients' characteristics were included in the analyses as predictors: sex, BMI (≤25; 25-30; >30 kg/m^2), smoking (never smokers, current smokers, ex-smokers), age of HS onset (≤30; 30-50; <50 years), age at diagnosis (dichotomised using the median value: ≤29; >29 years), age at baseline (≤30; 30-50; >50 years), therapeutic delay (dichotomised using the median value, that is ≤10 or >10 years), HS phenotypes, previous systemic retinoid therapy, previous systemic immunosuppressive/immunomodulating agents, systemic antibiotics concomitant with adalimumab. First, a univariate logistic regression analysis was performed. Subsequently, a multivariate model was fitted including only the variables significantly associated with the endpoint in the univariate analysis. The described univariate and multivariate regression approach were performed considering the two above-mentioned endpoints, in separate. Estimated odds ratios (OR) with their 95% confidence intervals (CI) were calculated from logistic regression parameters. Considering only patients with a complete follow-up (week 52), a paired analysis was performed to assess the change of DLQI and VAS pain scores from baseline to week 16 and to week 52. After having calculated variations of VAS pain and DLQI scores within each patient across the three time points, a Wilcoxon signed-rank test analysis was performed to assess the statistical significance of variations between baseline and week 16 and week 52. McNemar's test was used to compare the proportion of responders (HiSCR) at week 16 versus week 52. For descriptive purposes, a box plot was created showing time to treatment for responders and non-responders. P values lower than 0.05, two sided, were considered statistically significant. No correction for multiple testing was performed. All the statistical analyses were performed with the statistical software SAS (release 9.4, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Clinical features

Demographic and clinical features of the 389 patients at baseline are summarized in Table 1. Male patients were 50.6% (n=197/389) and the median age at baseline was 34 years. The median therapeutic delay was 10 years. A family history of HS was recorded in 81/388 patients (20.9%). Obesity was found in 104/385 patients (27%). Two hundred forty-six of 387 (63.6%) patients were current smokers, 36/387

(9.3%) were ex-smokers and 105/387 (27.1%) were never smokers. The main HS-related comorbidities included diabetes mellitus type II (n=25/389; 6.4%), acne vulgaris (n= 20/389; 5.1%), psoriasis (n=19/389; 4.9%) and inflammatory bowel diseases (16/389; 4.1%). Previous treatments included systemic antibiotics in 374/389 (96.1%) patients, systemic retinoids in 114/389 (29.3%) patients and immunosuppressive/immunomodulating agents (cyclosporine, systemic corticosteroids or dapsone) in 106/389 (27.3%) patients. Systemic antibiotics were administered in combination with adalimumab in 125/389 (32.1%) patients at different time points of the study to control disease flares. Two hundred and seventy-eight of 389 (71.5%) patients had a regular phenotype, 41/389 (10.5%) a conglobata phenotype, 33/389 (8.5%) a frictional furuncle phenotype, 21/389 (5.4%) a scarring folliculitis phenotype, 14/389 (3.6%) a syndromic phenotype and 2/389 (0.5%) an ectopic phenotype.

Response to adalimumab

All data about clinical response in terms of HiSCR at week 16 were available. HiSCR at week 52 was available for 308/389 (79.2%) patients, since 76 (19.5%) patients had not yet achieved this time point at the moment of data collection and data were missing in the remaining 5 (1.3%) patients. Clinical response to adalimumab assessed with HiSCR was achieved by 170/389 (43.7%) and 166/308 (53.9%) patients at week 16 and week 52, respectively. In 41 patients who had interrupted adalimumab before week 52 due to ineffectiveness (n=35) or adverse events/side effects (n=6), HiSCR at week 52 was considered as "not achieved". In fact, in the 6 patients who had experienced adverse events/side effects adalimumab was also ineffective.

The median IHS4, that was 17 at baseline, dropped to 10 at week 16 and to 8 at week 52 (Table 2). Time to treatment for responders and non-responders is shown in Figure 1.

Sex, BMI, age of onset, age at diagnosis, age at baseline, HS phenotypes and smoking correlated to response to adalimumab neither at week 16 nor at week 52. (Table 3) Interestingly, the therapeutic delay was identified as a significant risk factor for non-response to adalimumab in terms of HiSCR both at week 16 [OR, 1.92 for therapeutic delay $\geq$ 10 years; 95% CI, 1.28-2.89; P=0.0016] and at week 52 [OR, 1.60; 95% CI, 1.01-2.53; p= 0.0435].

Previous immunosuppressive/immunomodulating agents such as cyclosporine, systemic corticosteroids and dapsone inversely correlated to the response to adalimumab in terms of HiSCR at week 52 [OR, 1.78; 95% CI, 1.08-2.95; p=0.0250] but not at week 16 [OR, 0.97; 95% CI, 0.62-1.51; p=0.8765]. Considering the multivariate model including the two factors statistically significant at week 52 and adjusting for disease severity in terms of IHS4 at baseline, we found that only previous immunosuppressive/immunomodulating agents confirmed the statistical significance at multivariate

analysis. The inverse correlation found at univariate analysis between therapeutic delay and HiSCR at week 52 was not confirmed upon multivariate analysis [OR=1.59, 95%CI 0.99-2.55, p=0.055]. (Table 3)

When considering only the patients with complete follow-up (240/389 for DLQI and 253/389 for VAS pain), the median DLQI score, that was 20 at baseline, dropped to 10 at week 16 and to 7 at week 52. The median VAS pain score, that was 8 at baseline, dropped to 5 at week 16 and to 3 at week 52. (Table 2) We found a statistically significant reduction in DLQI scores between week 16 *versus* baseline ($p < 0.0001$), week 52 *versus* baseline ($p < 0.0001$) and week 52 *versus* week 16 ($p < 0.0001$). Likewise, we found a statistically significant reduction in VAS pain scores of week 16 *versus* baseline ($p < 0.0001$), week 52 *versus* baseline ($p < 0.0001$) and week 52 *versus* week 16 ($p < 0.0001$).

Safety

The majority of adverse events were mild in severity and most frequently included asthenia, headache, arthralgia, upper respiratory tract infection, dizziness, and nausea.

Five patients developed paradoxical skin reactions manifesting as psoriasis vulgaris (n=3), pustular psoriasis (n=1) and cutaneous vasculitis (n=1). Another patient developed alopecia areata.

No events of active tuberculosis, lymphoma, non-melanoma skin cancer, demyelinating disorder and no deaths were recorded. Three serious infections probably related to the treatment were reported in our cohort, including septicemia (n=2) and pneumonia sustained by *Aspergillus fumigatus* (n=1). Acute myocardial infarction occurred in a 39-year old male having multiple cardiovascular risk factors. Bladder cancer was diagnosed at week 40 after adalimumab initiation in a 52-year old male patient.

Adalimumab discontinuation

Adalimumab discontinuation (both temporary and definitive) was reported in 58/389 (14.9%) patients. Definitive discontinuation was observed in 41 (10.5%) patients, in 35 of whom drug withdrawal was due to lack or loss of clinical efficacy and in 6 of whom was due to severe adverse events/side effects (cancer, acute myocardial infarction, septicemia [n=2], pustular psoriasis, and cutaneous vasculitis).

Temporary discontinuation was observed in 17 (4.4%) patients, 9 of whom interrupted adalimumab to undergo surgical procedures on axillary, inguinal or gluteal areas and 8 of whom spontaneously discontinued adalimumab upon self-assessment of lack of effectiveness (n=4) or pregnancy (n=4). Two out of 389 (0.05%) patients were lost to follow-up.

DISCUSSION

Efficacy of adalimumab in the treatment of patients with moderate-to-severe HS refractory to conventional therapies, has been widely demonstrated in two 12-week controlled clinical trials.[13] Recently, two extension studies pointed out adalimumab 40 mg weekly as a reasonable approach also for medium-to-long-term control of moderate-to-severe HS. [14,15]

Notably, Bettoli *et al*. showed that HS duration and diagnostic delay negatively impact on disease severity[21] and, according to the "window of opportunity" hypothesis, it has been suggested that early treatment with adalimumab positively affects clinical response to the drug.[22] Likewise, early adalimumab treatment has been reported to be associated with better outcomes in both inflammatory bowel diseases and ankylosing spondylitis, reducing the risk of developing bowel strictures requiring intestinal surgery and irreversible bone damage leading to new bone formation, respectively.[23,24]

In HS, adalimumab should be started in a phase of the disease characterized by reversible lesions such as inflammatory nodules and abscesses before the development of lesions that cannot be reverted such as fistulas, sinus tracts and scarring sequelae.[22]

The main finding of our real-life study, conducted on a cohort of 389 patients with moderate-to-severe HS treated with adalimumab, is the significant inverse correlation between therapeutic delay and clinical response to the drug at week 16 of treatment. This may support early use of adalimumab in HS and provides evidence for a "window of opportunity" in this disease. Of note, the inverse correlation between therapeutic delay and clinical response was evident also at week 52 with univariate analysis but was not confirmed with multivariate analysis, albeit close to reaching statistical significance.

In our study, previous immunosuppressive/immunomodulating agents such as cyclosporine, systemic corticosteroids and dapsone, showed a statistically significant inverse correlation to the response to adalimumab at week 52, an intriguing, albeit hard to explain, finding that also fits in well with the early use of adalimumab. Theoretically, these agents could have influenced the immunological profile of our patients, inducing a switch to other non-TNF-driven inflammatory pathways, such as IL-17 and IL-23-related ones[11,25,26], and consequently interfering with the clinical behavior of the disease and response to adalimumab.

Clinical response to adalimumab assessed through HiSCR at week 16 and week 52 was achieved in 44% and 62% of patients, respectively, result that is in line with previously reported controlled clinical trials.[13-15] Interestingly, baseline DLQI and VAS pain scores showed a marked reduction at week 16, which progressed up to week 52, suggesting that improvement in patients' quality of life paralleled the clinical response, particularly in terms of IHS4.

On the other hand, it is of note that patients with great improvement in quality of life have shown a less evident clinical response in terms of HiSCR. This may be due to decrease in the inflammatory component

and volume of nodules/abscesses, along with decrease in purulent discharge from abscesses/fistulae, despite lack of reduction in the number of lesions.

On the other hand, sex, BMI, ages at onset/diagnosis/baseline, HS phenotypes and smoking were not associated with the clinical response to adalimumab. The lack of correlation between parameters such as BMI and smoking and clinical response to adalimumab is unexpected, considering that these factors seem to play a pathogenetic role and negatively impact on disease severity.[27,28] Actually, to the best of our knowledge there are no data in literature supporting that an increased BMI and/or smoking may impair the clinical response to adalimumab.

The safety profile of adalimumab in our cohort of patients was excellent, with only mild reported adverse events, including transient asthenia, headache, and nausea. Adalimumab discontinuation occurred in 14.9% of patients, mainly due to lack/loss of efficacy.

A limitation of this study is its retrospective and observational nature and the fact that the study population was limited to patients with moderate-to-severe HS resistant to standard first-line treatments according to the AIFA recommendations.

In summary, our findings indicate that adalimumab yields significant improvement in HS with a good safety profile, encouraging an early use of this drug to better control disease progression.

ACKNOWLEDGMENT

The authors wish to thank the following collaborators for their help in data analysis and patients' follow-up:

D. Abeni, P. Amerio, M. Barbareschi, P. Calzavara-Pinton, S. Calvieri, M.V. Cannizzaro, R.D. Caposiena Caro, M. Coppola, C. De Simone, M.T. Fierro, C. Foti, G. Giovanardi, G. Girolomoni, R. Giuffrida, E. Guanziroli, M. Iannone, M. Licciardello, C. Marasca, E. Molinelli, S. Muratori, M.L. Musumeci, G. Nazzaro, E. Passoni, A. Pavone, C. Peccianti, L. Pescitelli, G. Pistone, B. Raone, F. Ricceri, M. Romanelli, F. Rongioletti, P. Savoia, A. Sechi, S. Veraldi, M. Vispi

REFERENCES

1. Jemec GB. Clinical practice. Hidradenitis suppurativa. N Engl J Med 2012; 366:158-64.
2. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, Lapins J, Matusiak L, Prens EP, Revuz J, Schneider-Burrus S, Szepietowski JC, van der Zee HH, Jemec GB. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol 2015; 29:619-44.
3. Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In: Roenigk RK, Roenigk HH, editors. Dermatologic Surgery. Marcel Dekker, New York, 1989:729-739.
4. Shlyankevich J, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: a chart-verified case-control analysis. J Am Acad Dermatol 2014; 71:1144-1150
5. Saunte DM, Boer J, Stratigos A, Szepietowski JC, Hamzavi I, Kim KH, Zarchi K, Antoniou C, Matusiak L, Lim HW, Williams M, Kwon HH, Gürer MA, Mammadova F, Kaminsky A, Prens E, van der Zee HH, Bettoli V, Zauli S, Hafner J, Lauchli S, French LE, Riad H, El-Domyati M, Abdel-Wahab H, Kirby B, Kelly G, Calderon P, del Marmol V, Benhadou F, Revuz J, Zouboulis CC, Karagiannidis I, Sartorius K, Hagströmer L, McMeniman E, Ong N, Dolenc-Voljc M, Mokos ZB, Borradori L, Hunger RE, Sladden C, Scheinfeld N, Moftah N, Emtestam L, Lapins J, Doss N, Kurokawa I, Jemec GB. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol 2015; 173:1546-1549
6. Kolli SS, Senthilnathan A, Cardwell LA, Richardson IM, Feldman SR, Pichardo RO. Hidradenitis suppurativa has an enormous impact on patients' lives. J Am Acad Dermatol. 2019 Jul 11. pii: S0190-9622(19)32364-3. doi: 10.1016/j.jaad.2019.07.009. [Epub ahead of print]
7. Lima AL, Karl I, Giner T, Poppe H, Schmidt M, Presser D, Goebeler M, Bauer B. Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. Br J Dermatol 2016; 174:514-21.
8. Marzano AV, Damiani G, Ceccherini I, Berti E, Gattorno M, Cugno M. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). Br J Dermatol 2017; 176:1588-1598.
9. van der Zee HH, de Ruiter L, van den Broecke DG, Dik WA, Laman JD, Prens EP. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol 2011; 164:1292-8.
10. Matusiak L, Bieniek A, Szepietowski JC. Increased serum tumour necrosis factor-alpha in hidradenitis suppurativa patients: is there a basis for treatment with anti-tumour necrosis factor-alpha agents? Acta Derm Venereol. 2009; 89:601-3
11. Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with anti-IL-17 agents. J Am Acad Dermatol 2017; 76:670-675.

12. Thomi R, Cazzaniga S, Seyed Jafari SM, Schlapbach C, Hunger RE. Association of Hidradenitis Suppurativa With T Helper 1/T Helper 17 Phenotypes: A Semantic Map Analysis. JAMA Dermatol 2018; 154:592-595
13. 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; 375:422-34.
14. Zouboulis CC, Okun MM, Prens EP, Gniadecki R, Foley PA, Lynde C, Weisman J, Gu Y, Williams DA, Jemec GBE. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol 2019; 80:60-69.e2.
15. Jemec GBE, Okun MM, Forman SB, Gulliver WPF, Prens EP, Mrowietz U, Armstrong AW, Geng Z, Gu Y, Williams DA, Teixeira HD, Kimball AB. Adalimumab Medium-Term Dosing Strategy in Moderate-to-Severe Hidradenitis Suppurativa: Integrated Results from the Phase 3, Randomized, Placebo-Controlled, PIONEER Trials. Br J Dermatol. 2019 Mar 27 [Epub ahead of print]
16. van der Zee HH, Jemec GB. New insights into the diagnosis of hidradenitis suppurativa: Clinical presentations and phenotypes. J Am Acad Dermatol 2015; 73:S23-6.
17. Zouboulis CC, Tzellos T, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, Ingram JR, Kanni T, Karagiannidis I, Martorell A, Matusiak Ł, Pinter A, Prens EP, Presser D, Schneider-Burrus S, von Stebut E, Szepietowski JC, van der Zee HH, Wilden SM, Sabat R; European Hidradenitis Suppurativa Foundation Investigator Group. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol 2017; 177:1401-1409.
18. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19:210-6.
19. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17:45–56
20. Kimball AB, Sobell JM, Zouboulis CC, Gu Y, Williams DA, Sundaram M, Teixeira HD, Jemec GB. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. J Eur Acad Dermatol Venereol 2016; 30:989-94.
21. Bettoli V, Manfredini M, Calamo G, Forconi R, Bencivelli D, Mantovani L, Pellacani G, Corazza M. Long-term adalimumab treatment of hidradenitis suppurativa: Results and practical insights from a real-life experience. Dermatol Ther 2018; 31:e12737.
22. Martorell A, Caballero A, González Lama Y, Jiménez-Gallo D, Lázaro Serrano M, Miranda J, Pascual JC, Salgado-Boquete L, Marín-Jiménez I. Management of patients with hidradenitis suppurativa. Actas Dermosifiliogr 2016; 107:32-42.

23. Safroneeva E, Vavricka SR, Fournier N, Pittet V, Peyrin-Biroulet L, Straumann A, Rogler G, Schoepfer AM; Swiss IBD Cohort Study Group. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. Aliment Pharmacol Ther 2015; 42:977-89.
24. Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis 2013; 72:23-8.
25. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011; 65:790-798.
26. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model. Front Immunol. 2018; 9:2965.
27. Melnik BC, John SM, Chen W, Plewig G. T helper 17 cell/regulatory T-cell imbalance in hidradenitis suppurativa/acne inversa: the link to hair follicle dissection, obesity, smoking and autoimmune comorbidities. Br J Dermatol 2018; 179:260-272.
28. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the U.S.A. Br J Dermatol 2018; 178:709-714.

Table 1. Patients' demographic and clinical features (n=389)

Age at onset (years) *		20 (16-28)
Age at diagnosis (years)*		29 (21-37)
Age at baseline (years) *		34 (25-46)
Therapeutic delay (years) *		10 (5.8-20)
Males, N (%)		197 (50.6)
Body mass index, N (%) §	**≤25 kg/m²**	149 (38.7)
	25-30 kg/m²	132 (34.3)
	>30 kg/m²	104 (27)
Current smokers, N (%) §§		246 (63.6)
Family history of hidradenitis suppurativa, N (%) §§§		81 (20.9)
Previous systemic antibiotics, N (%)		374 (96.1)
Previous systemic retinoids, N (%)		114 (29.3)
Previous systemic immunosuppressive/immunomodulating agents, N (%)		106 (27.3)
Systemic antibiotics concomitant with adalimumab, N (%)		125 (32.1)
Hidradenitis suppurativa phenotypes, N (%)	**Regular**	278 (71.5)
	Frictional furuncle	33 (8.5)
	Scarring folliculitis	21 (5.4)
	Conglobata	41 (10.5)
	Syndromic	14 (3.6)
	Ectopic	2 (0.5)

** Data are reported as median (IQR)*

§ Data on Body Mass Index were missing in 4 patients

§§ Data on smoking were missing in 2 patients

§§§ Data on family history of hidradenitis suppurativa were missing in 1 patient

Table 2. International Hidradenitis Suppurativa Severity Score System (IHS4), Dermatology Life Quality Index (DLQI), Visual Analogue Scale for pain (VAS pain) and Hidradenitis Suppurativa Clinical Response (HiSCR) scores at baseline, week 16 and week 52

	Score Baseline	Score Week 16	Score Week 52
International Hidradenitis Suppurativa Severity Score System* (N=265)	17 (11-27)	10 (7-18)	8 (4-12)
Dermatology Life Quality Index* (N=240)	20 (12-25)	10 (7-18)	7 (4-14)
Visual Analogue Scale for pain* (N=253)	8 (6-9)	5 (3-6)	3 (2-5)
HiSCR ****	NA	170 (43.7)	166 (53.9)

**Data are reported as median (IQR). Only patients with complete follow-up data have been included in this analysis.*

***Data are reported as number of patients (percentage)*

N= number of patients included in the analyses; exclusion reasons are ongoing therapy at the moment of data collection, drug interruption or missing data

NA: not applicable

For IHS4, DLQI and VAS-pain, all p values for pairwise comparisons between t52 and t16 versus baseline are < 0.0001

For HiSCR p value is 0.0004

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for non-response to adalimumab according to baseline clinical parameters in patients with moderate-to-severe hidradenitis suppurativa at week 16 and week 52

		Week 16 (n=389)			Week 52§§ (n=308)		
		OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Sex	Females	1 *		0.9849	1 *		0.5860
	Males	1	0.67-1.5		0.88	0.56-1.38	
Age at hidradenitis suppurativa onset	>50	1 *		0.8997	1 *		0.7608
	30-50	1.39	0.32-6.05		1.39	0.28-6.95	
	<=30	1.28	0.31-5.20		1.11	0.24-5.04	
Age at diagnosis	<=29	1*		0.181	1*		0.8861
	>29	1.32	0.88-1.97		0.97	0.62-1.52	
Age at baseline	>50	1 *		0.1338	1 *		0.3284
	30-50	0.63	0.34-1.15		0.71	0.37-1.33	
	<=30	0.53	0.28-0.99		0.61	0.32-1.17	
Body Mass Index	≤25	1 *		0.9080	1 *		0.4293
	25-30	1.08	0.67-1.72		1.39	0.82-2.36	
	>30	1.11	0.67-1.85		1.32	0.75-2.33	
Smoking	Never smokers	1 *		0.4763	1 *		0.4897
	Current smokers	1.18	0.75-1.87		0.77	0.46-1.29	
	Ex-smokers	1.61	0.74-3.51		1.07	0.47-2.43	
Therapeutic delay, years §	<10	1 *		0.0016	1 *		0.0435
	≥10	1.92	1.28-2.89		1.60	1.01-2.53	
Hidradenitis suppurativa phenotypes	Regular	1 *		0.5630	1 *		0.8484
	Frictional furuncle and scarring folliculitis	1.38	0.76-2.53		1.11	0.57-2.15	
	Conglobata and ectopic	1.05	0.59-1.86		0.86	0.44-1.69	
Previous systemic retinoids	No	1 *		0.6245	1 *		0.8987
	Yes	0.90	0.58-1.39		1.03	0.63-1.69	
Previous systemic immunosuppressive/immunomodulating agents	No	1 *		0.8765	1 *		0.0250
	Yes	0.97	0.62-1.51		1.78	1.08-2.95	
Systemic antibiotics concomitant with adalimumab	No	1 *		0.0597	1 *		0.7266
	Yes	1.52	0.98-2.35		1.09	0.68-1.75	

** Reference category*

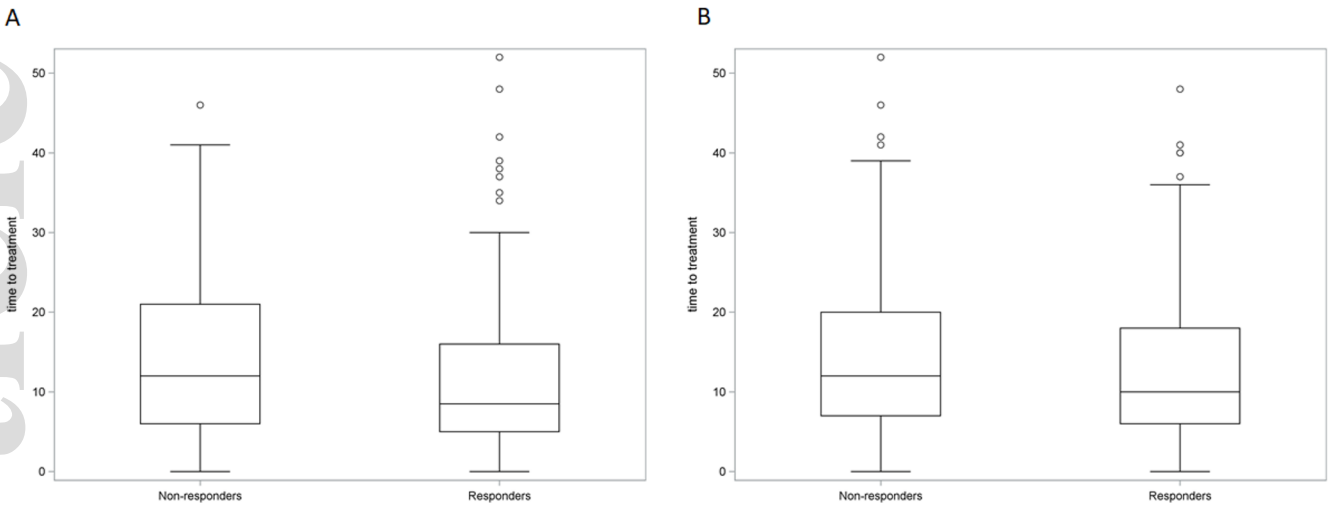
§ Effect of therapeutic delay at week 16 in regression analysis adjusted for disease severity in terms of IHS4 at baseline: OR 1.81, 95%CI 1.20-2.74, p=0.0046

§§At multivariate analysis, including "Therapeutic delay" and "Previous systemic immunosuppressive/immunomodulating agents" and adjusted for disease severity in terms of IHS4 at baseline, the following results were obtained

- "Therapeutic delay" (<=10 vs >10 years): OR=1.59, 95%CI 0.99-2.55, p=0.055;

- "Previous systemic immunosuppressive/immunomodulating agents" (Yes vs No): OR=1.74, 95% CI 1.04-2.91, p=0.0342

Figure 1. Box plot summarising the distribution of time to treatment for responders and non-responders (clinical response assessed using the Hidradenitis Suppurativa Clinical Response). Panel A: response at week 16; panel B: response at week 52. The horizontal line within the box represents the median value for time to treatment; the upper horizontal line of the box represents the 3rd quartile (Q3); the lower horizontal line of the box represents the 1st quartile (Q1). Upper fence is Q3+1.5 IQR; lower fence is the minimum observed value. Dots represent outliers.



bjd_18983_f1.tif