Journal of Dermatological Treatment

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

Seven Years-Experience of adalimumab therapy for hidradenitis suppurativa in a real-life dermatologic setting

G. Odorici, L. Pacetti, R. Forconi, N. Schettini, P. Zedde, M. Corazza & V. Bettoli

To cite this article: G. Odorici, L. Pacetti, R. Forconi, N. Schettini, P. Zedde, M. Corazza & V. Bettoli (2021): Seven Years-Experience of adalimumab therapy for hidradenitis suppurativa in a real-life dermatologic setting, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2021.1914309

To link to this article: https://doi.org/10.1080/09546634.2021.1914309

Accepted author version posted online: 12 Apr 2021.

Seven Years-Experience of Adalimumab Therapy for Hidradenitis Suppurativa in a Real-life Dermatologic Setting

Authors:
G. Odorici,[1] L. Pacetti,[1] Forconi R,[1] N. Schettini, [1] P. Zedde, [1] M. Corazza, [1] V. Bettoli[1]

[1]Department of Medical Sciences, Section of Dermatology and Infectious Diseases
University of Ferrara, Ferrara, Italy.

Corresponding author:
Dr. Giulia Odorici
Department of Medical Sciences, Section of Dermatology and Infectious Diseases
University of Ferrara
Via L. Ariosto 35, 44121, Ferrara, Italy
Tel: (+39) 0532/239684 Fax: 0039 0532/206791
E-mail: giulai87@hotmail.com

Manuscript word count: 2500
Figure count: 0
Table count: 2
References: 22

Funding sources: None.
Conflict of interest: The authors have no conflicts of interest to disclose.
Keywords: Idradenitis suppurativa, adalimumab, therapy, biologic, biosimilar

Acknowledgments: Honorarium, grant, or other form of payment were not given to anyone of the authors to produce the manuscript. All authors made substantive intellectual contributions to the published study and each author listed on the manuscript has seen and approved the submission of the manuscript

Abstract

Introduction: Hidradenitis Suppurativa (HS) often causes severe impairment of the quality of life of patients affected, as it is characterized by recurrent relapses of inflammation and predisposes to retractive scars, with severe alteration of anatomy of the affected regions. Adalimumab is currently the only approved long-term biological therapy for this disease.

Material and method: we retrospectively review the data of HS patients treated with Adalimumab at the "Hidradenitis Suppurativa Clinic", University of Ferrara, Italy since the drug was first available to October 2020. The aim is to describe our real-life experience in a clinical outpatient service. We assessed the main demographic features, therapy duration, reasons of suspension and efficacy (evaluated by HiSCR – Hidradenitis Score) in relation to surgical procedures, hospitalization, number of areas involved by the disease and BMI > 30. We also assessed the aspects related to the use of adalimumab's biosimilar.

Results: data on 76 patients, with a mean age of 38.26 ± 14.74 years and mean BMI 28.10 ± 5.92 were collected. Most of the treated patients had Hurley stage III (58/76); mean Sartorius score was 115.5 ± 55.86, mean IHS4 was 76.1 ± 44.3. A statistically significant correlation between hospitalization and cessation of adalimumab, the loss of the achievement of the HiSCR, and surgery was found. No need to do surgery was a protective factor against the failure of adalimumab treatment, meaning that the most severe cases are more likely to fail the biological therapy.

Conclusion: new scenarios are opening up in clinical practice: the arrival of biosimilars allow greater sustainability of expenditure, while the anti-IL17 allow the patient who has failed therapy with adalimumab a valid and safe therapeutic option to be undertaken. A comprehensive care including hospitalization, a specific antibiotic therapy and surgical treatment is often mandatory to achieve a satisfactory control of the disease.

Introduction: Hidradenitis Suppurativa (HS) often causes severe impairment of the quality of life of patients affected. Adalimumab is currently the only approved long-term biological therapy for this disease.

Material and method: we retrospectively review the data of HS patients treated with Adalimumab, since it was first available to October 2020, aimed to describe our real-life experience in a clinical outpatient service. We assessed the main demographic features, therapy duration, reasons of suspension and efficacy (evaluated by HiSCR – Hidradenitis Score) in relation to surgical procedures, hospitalization, number of areas involved by the disease and BMI > 30. We also assessed to the use of adalimumab's biosimilar.

Results: data on 76 patients, with a mean age of 38.26±14.74 years and mean BMI 28.10±5.92 were collected. Most of the treated patients had Hurley stage III (58/76); mean Sartorius score was 115.5±55.86, mean IHS4 was 76.1±44.3. A statistically significant correlation between hospitalization and cessation of adalimumab, the loss of the achievement of the HiSCR, and surgery was found.

Conclusion: new scenarios are opening up in clinical practice: the arrival of biosimilars allow greater sustainability of expenditure. A comprehensive care is often mandatory to achieve a satisfactory control of the disease.

Hidradenitis suppurativa (HS) is a chronic, recurrent and poorly understood debilitating disease, often causing severe impairment of the quality of life of patients affected as well as their family members and caregivers.[1]

Its pathogenesis is not completely understood, depending on innate and adaptive immune dysregulation, keratinocytes hyper-proliferation and occlusion of the pilo-sebaceous follicles.[2]

It is believed that the primary event in the evolution of the disease is the follicular hyperkeratosis, followed by hair follicle plugging and dilatation, rupture of the follicle with inflammatory / immunological reaction characterized by macrophages, neutrophils, B and T lymphocytes. In a second stage, chronic inflammation occurs with possible bacterial super-infections and the secondary involvement of the apocrine glands.[3,4]

For the most part, HS is a difficult-to-manage disease, and, although several drugs and surgical approaches are available to date, important unmet medical needs are still present. The therapeutic approaches include anti-inflammatory, antibiotic and immune-modulatory agents, including biologics.[5]

Antibiotics and biologics are the most used treatment in the real-life setting, due to the favorable risk-benefit ratio. Antibiotics can be useful for improving disease severity and to manage over-infections, but they can be administered for a relatively short period of time, so the long-term efficacy of such a therapy is limited. Adalimumab, the only biologic drug approved to date, is a valid and efficacious choice in the long-term treatment.[6,7]

Despite a good response could be achieved combining or sequencing these therapies, the surgical approach is often mandatory, due to the scarring evolution often observed in many patients.[8]

Since the beginning of the "Acne and Hidradenitis Suppurativa Clinic", of Dermatology Unit, Azienda Ospedaliera University of Ferrara we followed-up 841 first-seen patients suffering from HS in the out-patients service.

This paper aims to describe the personal experience in the treatment of HS with adalimumab, in order to offer an overview of a real-life experience and the insights we have achieved while treating such a complex disease. We will discuss how demographic data, clinical features, comorbidities and previous or concomitant antibiotic therapy influenced the efficacy and the duration of the treatment. In addition, treatment-related adverse events, hospitalization, surgical therapy and the switch to a biosimilar or to another biological drug have been taken into consideration.

Study design and patients:

This is a real-life retrospective observational study on patients affected by HS who were treated with adalimumab at the "Hidradenitis Suppurativa Clinic", Dermatology Unit, of the Azienda Ospedaliera - University of Ferrara, Italy, from September 2013 to October 2020.

Data were gathered from the computer database of the outpatient service. Inclusion criteria were: patients affected by HS treated with adalimumab, followed-up for at least 6 months with at least 3 visits. Combination of adalimumab with topical agents or systemic drugs for HS did not represent an exclusion criterion. Adalimumab was administered subcutaneously at the standard labelled dosage for HS (40 mg / weekly). At baseline, we registered demographic data, BMI, HS medical history, HS duration, Hurley stage, Sartorius and IHS4 scores, smoking habit, comorbidities, previous systemic and surgical therapies. The patients were revaluated on average every 3 months, performing at every medical examination a clinical evaluation of the severity of the disease, and the safety lab tests recommended by the guidelines. The occurrence of hospitalization, surgical treatment, efficacy or loss of efficacy of the treatment and the achievement of the HiSCR (defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline) were also recorded.[9,10]

Descriptive statistics and complete case analysis were used for all comparisons between groups. The results are presented as the mean ± standard deviation (SD) for continuous variables, as percentages for categorical variables. Pearson's chi-square test and Fisher's exact test were used to reveal associations between variables and groups. Univariate and multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) between groups for all variables. Statistical analysis was performed using STATA® software version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). For all tests, a $p<0.05$ was considered statistically significant.

Results:

We describe 76 patients treated with adalimumab, from September 2013 until 31 October 2020. They were 40 men and 36 women, with a mean age of 38.26 ± 14.74 years, mean BMI 28.1 ± 5.92. Sixty-one of them had a history of smoking (10.2 ± 9.25 cigarettes per day), and 40 of them presented comorbidities (Table 1). Adalimumab was started 15.63 ± 14.31 years after the onset of the disease, which occurred at a mean age of 22.63 ± 11.31 years. Regarding the comorbidities (listed in table 1), 2 patients had had hepatitis B and 2 latent TBC (underwent prophylaxis according to guidelines) with no signs or symptoms of reactivation during the period of treatment with adalimumab. The affected areas were the classical ones, including axillae, sternal, sub-mammary, groin, gluteal, genital and perianal. In some cases also the abdomen and the back were involved. Most of the treated patients had Hurley stage III (58/76); mean

Sartorius score was 115.5 ± 55.86, mean IHS4 was 76.1 ± 44.3. They were all treated with at least 3 antibiotics prior to start the biological therapy. Moreover, 35 patients received further prior systemic treatments such as retinoids, immunosuppressor (cyclosporine, metotrexate or steroids) or anti-androgen drug (finasteride). Twenty-nine of them were hospitalized due to the severity of the disease and the presence of skin superinfections. During this period they were treated with intravenous antibiotics on the basis of the cutaneous swabs performed at admission. Twenty-three patients also underwent surgery during adalimumab therapy. Surgery was always performed on the areas were the HS was more severe but also approachable. Twenty-four patients interrupted the treatment with adalimumab due to inefficacy (HiSCR not achieved), loss of efficacy or side effects / comorbidities that contraindicated the continuation of the biological treatment (1 patient developed a retrobulbar optic neuritis, 1 arthritis, 1 myositis, 1 muscles aches, 1 cutaneous squamous cell carcinoma, 1 anemia and chronic renal failure, 1 refractory anemia, 1 recurrent cystitis, 1 fever after injections, 1 nausea and 1 asthenia related to the therapy).

Twelve out of 76 patients either spontaneously interrupted the follow-up visits or chose to be followed by another center due to geographical reasons. One patient passed away because of an acute cardiovascular condition not related to the drug.

The mean duration of adalimumab therapy was 20.36 ± 16.34 months in the patients who discontinued the treatment due to inefficacy or adverse events, while 23.38 ± 14.14 months was the mean duration of treatment for the ones still on treatment. One patient, affected by moderate-severe HS achieved complete and stable remission of the disease, after 3 years of therapy.

The patients who underwent surgery in at least one affected area had a longer time of adalimumab assumption, although this data was not statistically significant (24.61 ± 15.27 months vs 21.20 ± 15.37 months).

Six patients started the biological therapy with a biosimilar drug, according to regional Health Authorities suggestions, while 4 switched during treatment. Two of the latter switched back to Humira® due to intolerance to the biosimilar (because of local reaction at the site of subcutaneous injection).

Among those who interrupted Adalimumab, 10 are now in treatment with an anti IL-17 biologic, either performing a trial or on an off-label modality.

We found a positive statistically significant correlation between the involvement of 5 body areas and the BMI > 30 ($p= 0.0408$), between the hospitalization and surgery ($p= 0.0072$), and no achievement of HiSCR ($p= 0.0010$), between stop of the treatment and hospitalization ($p= 0.0139$), and surgery ($p= 0.0447$) (Table 2).

In consideration of the peculiar times in which we have performed this retrospective data collection, we also report, as a safety issue, that only one patient, a 24-year old male, resulted affected by SARS-CoV-2 however completely asymptomatic. He did not suspend the therapy and became negative after 18 days from the fist molecular swab performed.

Discussion

HS is one of the most debilitating dermatoses, usually presenting after puberty and clinically characterized by painful nodules, abscesses, sinus tracts (tunnels) and scars, with chronic and recurrent relapses and the involvement of large areas (typically the axillary, infra-mammary and inguinal folds, but also neck, torso, pubis and genitals). The innate and acquired immunity are involved in the onset and maintenance of the disease. Histologically the disease is characterized by an occlusion of the hair follicles, with the release of keratin and bacteria in the dermis, followed by a foreign body reaction and a chemotactic inflammatory response characterized by neutrophils and lymphocytes that lead to abscess formation and subsequent destruction of the pilosebaceous unit and other adjacent structures. Obesity and smoking, often observed in patients suffering from HS, can play a favoring role in the production of pro-inflammatory cytokines, both through immunological effects and epithelial hyperplasia and acanthosis.[4] Adalimumab is the first fully human recombinant immunoglobulin G1 monoclonal antibody, acting as a tumor necrosis alpha factor (TNF-alpha) inhibitor, selectively binding and neutralizing soluble and membrane-bound TNF-alpha. It also induces apoptosis in mononuclear cells with TNF-alpha receptors. It is considered the first-line biologic therapy in HS, after failure of conventional treatment. It has a well-established long-term safety profile, as it is used for many conditions. The established side effects are the reactivation of tuberculosis, viral hepatitis, and other skin reactions such as worsening of psoriasis. The HS regimen encloses an injection of 160 mg at day 0, followed by 80 mg at day 14 and an injection of 40 mg every week since day 28.[5,11]

Adalimumab is a useful treatment in HS, either on its own, in combination with surgical treatment or sequentially with other classes of drugs. In our experience, all patients had been treated with at least two systemic therapies prior to adalimumab (including at least 1 antibiotic).

A long time can pass between the time of onset and that of diagnosis of HS, often causing a worsening of the clinical picture. The severity is sometimes associated to a stigmatization of the affected patients. The course of the disease may vary, and it is recognized that in almost 1/3 of the patients the disease can improve, in 1/3 it remains stable, and in 1/3 it may worsen over time.

We observed that the discontinuation of the therapy was statistically related to hospitalization, which is connected to the failure to achieve the HiSCR. During their stay as in-patients, specific intravenous antibiotic therapy was administered on the basis of cutaneous swabs and microbiological results. This lead us to suppose that specific antimicrobial treatment is needed before starting a biologic drug, as this may have a direct antibiotic effect and can help modulating the inflammatory / immunological response. When superinfections are not adequately controlled, the biologic therapy alone may mistakenly appear unsuccessful and the patients tend to stop the treatment, as it is not considered beneficial.

Moreover, obesity (BMI>30) was related to the involvement of at least 5 anatomical areas and this last aspect was statistically related to the interruption of the drug for inefficacy. Discontinuation of adalimumab is statistically related to surgery, meaning that the very severe cases, including the presence of scars, do not improve with the biologic alone, and surgery has to be offered early, to prevent the inefficacy of the therapy in selected patients. In this work, we included a large part of patients affected by Hurley III stage of disease, but in our clinical practice we often propose the surgical approach specifically in patients with Hurley I, where we usually observe a good result with long time remission of HS.

Biosimilars show good tolerance and efficacy that make them useful and safe; to date, they are widely used in real life practice, although their indications are "extrapolated" from trials on other diseases in which adalimumab originator was used.

There are still few patients who have started biosimilar therapy, and for this reason it is not possible to draw conclusions on its long-term efficacy. Moreover, in our country, the prescription is subject to regional variabilities; this makes it hard to compare the various types of biosimilar products. To date, most clinicians believe that keeping the originator drug for those who already reached clinical stability with it and reserve the biosimilar for naïve patients is the wisest approach.

The data underlines the importance of a comprehensive care, while keeping in mind that HS is a complex disease where every patient is characterized by a different clinical presentation, that can vary over time.[12]

Sometime the disease has prevalent infectious complications and sometimes need a surgical approach.[13]

The physician should evaluate these variables in order to offer the best approach (including specific antibiotic therapy, biologics and surgery) in the right time.

References:

1) Muralidharan V, Pathmarajah P, Peterknecht E, et al. Real life data on the biopsychosocial effects of Adalimumab in the management of hidradenitis suppurativa: A multicenter cross sectional analysis and consideration of a multisystem monitoring approach to follow up. Dermatol Ther. 2020 Dec 9:e14643.
2) Dunstan RW, Salte KM, Todorović V, et al. Histologic Progression of Acne inversa/hidradenitis suppurativa: Implications for future Investigations and therapeutic intervention. Exp Dermatol. 2020 Dec 30. doi: 10.1111/exd.14273. Online ahead of print.
3) Wolk K, Join-Lambert O, Sabat R. Aetiology and pathogenesis of hidradenitis suppurativa. Br J Dermatol. 2020 Dec;183(6):999-1010.
4) Zouboulis CC, Benhadou F, Byrd AS, et al. What causes hidradenitis suppurativa ?-15 years after. Exp Dermatol. 2020 Dec;29(12):1154-1170.
5) Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization: systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol. 2019;33:19–31.
6) van der Zee H, Longcore M, Geng Z, Garg A. Weekly adalimumab treatment decreased disease flare in hidradenitis suppurativa over 36 weeks: integrated results from the phase 3 PIONEER trials. J Eur Acad Dermatol Venereol. 2020;34(5):1050–6.
7) Tzanetakou V, Stergianou D, Giamarellos-Bourboulis EJ. Long-term safety of adalimumab for patients with moderate-to-severe hidradenitis suppurativa. Expert Opin Drug Saf. 2020 Apr;19(4):381-393.
8) Blok JL, van Hattem S, Jonkman MF, Horváth B. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br J Dermatol. 2013;168:243–52.
9) Kimball AB, Sobell JM, Zouboulis CC, Gu Y, Williams DA, Sundaram M, et al. 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.
10) Kimball AB, Jemec GBE, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol. 2014;171:1434–42.
11) J.R. Ingram, P.N. Woo,2S.L. Chua, et al. Interventions for hidradenitis suppurativa: a Cochrane systematic review incorporating GRADE assessment of evidence quality

12) Cazzaniga S, Pezzolo E, Bettoli V, et al. Characterization of Hidradenitis Suppurativa Phenotypes: A Multidimensional Latent Class Analysis of the National Italian Registry IRHIS. J Invest Dermatol. 2020 Oct 21:S0022-202X(20)32184-9.

13) Marzano AV, Genovese G, Casazza G, et al. Evidence for a 'window of opportunity' in hidradenitis suppurativa treated with adalimumab: a retrospective, real-life multicentre cohort study. Br J Dermatol. 2021 Jan;184(1):133-140

<table>
<tr><td rowspan="5">Demographic</td><td>Gender</td><td>36 F
40 M</td><td rowspan="10">Comorbidities</td><td>Dermatologic</td><td>7 acne
4 pilonidal cyst
3 psoriasis</td></tr>
<tr><td>Disease onset (age in years)</td><td>22.63 ± 11.31</td><td rowspan="2">Cardiovascular</td><td rowspan="2">5 hypertension
3 ischemic attack
1 dilated cardiomyopathy
1 atrial fibrillation</td></tr>
<tr><td>Age at baseline (years)</td><td>38.26 ± 14.74</td></tr>
<tr><td>Smoke habits</td><td>47 Yes</td></tr>
<tr><td>BMI</td><td>28.10 ± 5.92</td></tr>
<tr><td>HS characteristics</td><td>Area affected (n of patients)</td><td>47 axillae
64 groin
14 Inframammary fold
24 pubis
17 genital
26 gluteal
19 perianal
14 trunk</td><td>Metabolics</td><td>5 diabetes
1 dyslipemia
3 hyper insulinemia</td></tr>
<tr><td rowspan="2">Mean duration of therapy</td><td>in the patients who discontinue the treatment</td><td>20.36 ± 16.34 months</td><td rowspan="2">Auto-immune</td><td rowspan="2">1 pyoderma grangrenosum
1 RCU + ileostomy
1 autoimmune thrombocytopenia
1 folliculitis decalvans
1 peripherical arthritis
2 alopecia areata</td></tr>
<tr><td>Patient who continue the treatment</td><td>23.38 ± 14.14 months</td></tr>
<tr><td colspan="2">Adverse events occurred during the treatment</td><td>1 retrobulbar optic neuritis
1 arthritis
1 myositis
1 muscles aches
1 cutaneous squamous cell carcinoma
1 anemia and chronic renal failure
1 refractory anemia
1 recurrent cystitis
1 fever after injections
1 nausea
1 asthenia</td><td>infectious</td><td>2 tuberculosis
2 chronic hepatitis (HBV or HCV)</td></tr>
<tr><td colspan="3"></td><td>neurological</td><td>1 epilepsy</td></tr>
<tr><td colspan="3"></td><td>other</td><td>1 benign prostate hypertrophia
1 megaureter
1 squamous cell carcinoma
2 refractory anemia
1 Keratitis-ichthyosis-deafness syndrome (KID)</td></tr>
</table>

Table 1: Demographic, comorbidities and therapy characteristics of patients treated with Adalimumab

	YES	NO	p-value	OR		YES	NO	p-value	OR		YES	NO	p-value	OR		YES	NO	p-value	OR
Sex (F; M)																			
Hospitalization	9	20	0.02508	0.33	Surgery	10	13	0.6545	1.07	StopAda	9	15	0.2417	0.67	BMI>30	9	13	0.4716	0.77
Smoke																			
Hospitalization	17	12	0.3007	0.74	Surgery	17	6	0.3254	0.86	StopAda	19	5	0.0949	1.98	BMI>30	17	5	0.1780	1.77
1 Area affected																			
Hospitalization	1	28	1	0.64	Surgery	3	20	0.0801	0.35	StopAda	0	24	NA	0	BMI>30	0	22	NA	0
2 Areas affected																			
Hospitalization	9	20	0.519	1.83	Surgery	5	18	0.7624	0.95	StopAda	6	18	0.5373	1.36	BMI>30	2	20	0.206	0.41
3 Areas affected																			
Hospitalization	10	19	0.2168	0.69	Surgery	8	15	0.3168	1.16	StopAda	8	16	0.2280	0.65	BMI>30	10	12	0.0521	1.09
4 Areas affected																			
Hospitalization	4	25	0.1111	0.52	Surgery	8	14	0.1227	0.73	StopAda	8	16	0.3339	1.61	BMI>30	6	16	0.9617	1.21
5 Areas affected																			
Hospitalization	4	25	0.1943	1.87	Surgery	4	19	0.2344	0.69	StopAda	3	21	0.702	1.21	BMI>30	5	17	0.0408	2.5
Hospitalization																			
					Surgery	14	9	0.0072	0.64	StopAda	14	10	0.0139	2.27	BMI>30	10	12	0.4032	1.35
HiSCR reached																			
Hospitalization	5	24	0.001	0.3	Surgery	8	15	0.4827	1.11	StopAda	1	23	0.00001	0.06	BMI>30	8	14	0.6162	0.83
Surgery																			
Hospitalization	14	15	0.0072	2.15						StopAda	11	13	0.0447	1.95	BMI>30	8	14	0.4599	1.32
Adalimumab stopped																			
Hospitalization	14	15	0.0139	2.02	Surgery	11	13	0.0447	0.69						BMI>30	9	13	0.2640	1.35
BMI>30																			
Hospitalization	10	34	0.1609	0.72	Surgery	8	14	0.3628	0.8	StopAda	9	15	0.2640	1.47					

Table 2: statistical analysis of items considered