

ADOLESBIO-HS: A Real-World Multicenter Case Series on the Effectiveness and Safety of Adalimumab in Adolescents with Moderate-to-Severe Hidradenitis Suppurativa

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Keywords

Dermatology · Hidradenitis suppurativa · Drug response · Adalimumab · Adolescence · Pediatric

Abstract

Introduction: Hidradenitis suppurativa (HS) is a chronic disease that causes painful skin lumps and scarring in the skin. In an important number of patients, the disease starts in adolescence. Adalimumab was the first biologic drug approved in adolescents with HS, yet approval was done on a model-based extrapolation from other diseases. Data regarding the effectiveness and safety of adalimumab in HS in this age group is lacking. Our objective was to describe the effectiveness and safety of adalimumab in adolescents with

moderate-to-severe HS. **Methods:** Retrospective multicenter case series. HS units across Spain were invited to participate, including all patients starting adalimumab in adolescence. Demographic, clinical, and treatment-related characteristics were retrieved. Effectiveness was measured as the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at 6 months. Safety was assessed by means of quantification and description of side effects over time. **Results:** A total of 65 patients from 9 HS units were included. Mean age at adalimumab start was 15.5 years. A total of 76.9% of patients achieved HiSCR at 6 months. Side effects were observed in 7 patients, 3 of them requiring drug discontinuation, with full recovery. The adult dosage (80 mg every other week [EOW]/40 mg every week) was more frequently used. The median drug survival time for adalimumab

was 5.6 years (25th percentile: 2.9 years), and the recommended adolescent dosage (40 mg EOW) was associated with a need for intensification ($p < 0.001$). The main limitations of the study are the lack of a comparison group and the retrospective design. **Conclusion:** Adalimumab showed a similar safety profile in adolescents with moderate-to-severe HS as in adults, with better effectiveness data.

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Introduction

Hidradenitis suppurativa (HS) is a chronic debilitating skin condition, with an important impact on quality of life [1]. Severe pain, malodor and discharge are often associated with HS lesions, leading to physical and psychological distress [2, 3]. In an important number of patients, the disease starts in adolescence [4, 5]. Early treatment in HS is essential to decrease morbidity [6]. In 2015, Adalimumab became the first biological drug approved for adults with moderate-to-severe HS based on the results of the PIO-NEER trials [7], at a dosage of 40 mg every week (EW). Later on, adalimumab received approval for adolescents aged 12–18 years in Europe [8], and in the USA, in both regions at half the dosage approved in adults, i.e., 40 mg every other week (EOW). However, this extension of approval in adolescents was based on extrapolation from other diseases and on a model-informed basis [9], yet clinical real data about the effectiveness and safety of adalimumab in this age group in HS patients was missing [10]. A recent systematic review on the efficacy of medical treatments for pediatric HS underscored the need of real clinical data in this disease, as it could only collect data on 33 patients, was mainly based on case reports and short case series, and included different biologics (adalimumab, infliximab, anakinra, etanercept, and ustekinumab), rendering quantification of response unmeasurable [11], with safety data being even scarcer. The objective of this study was to describe the effectiveness, the dosage and the safety of adalimumab in adolescents with moderate-to-severe HS, in a real-world setting.

Methods

Study Design and Assessments

We performed a retrospective multicenter case series across Spain. Hospitals with an HS unit were invited to participate in July 2023, and data collection was carried out until October 2023. Electronic medical records of all adolescent patients receiving adalimumab treatment within

participating HS units were reviewed. De-identified demographic and clinical data were extracted. Following the World Health Organization's definition of adolescence, which encompasses individuals aged 10–19 years [12, 13], we included patients who initiated adalimumab treatment within this age range. Patients who had not yet completed 6 months of treatment at the time of data collection – due to having recently initiated therapy – were excluded. However, patients who discontinued treatment before 6 months for other reasons such as side effects were included.

Outcome measures were effectiveness and safety of adalimumab treatment. Effectiveness was measured as the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at 6 months. HiSCR is a validated outcome measure in HS and is defined as reduction of at least 50% in the total abscess and inflammatory nodule count, with no increase in abscess count and no increase in draining fistula count, relative to baseline [14]. The need for dose change (intensification or de-intensification) over time was also retrieved, in order to assess which starting dose could be more effective in this age group, also in the mid and long term. Safety was assessed by means of quantification and description of side effects over time overall, by age subgroup, and by adalimumab starting dose.

Exposure variables included sex, family history of HS, age, disease duration and severity at adalimumab start, smoking habit, body mass index (BMI), Hurley stage, anatomic locations of disease, adalimumab dosage (the “adolescent” dosage: 40 mg EOW, or the “adult” dosage, which included the 40 mg EW and the equivalent 80 mg EOW regimes, this latter having been introduced later, with better acceptability among patients [15, 16]), and previous treatments. Disease severity was assessed by means of the International Hidradenitis Suppurativa Severity Score System (IHS4), a validated tool to dynamically assess severity in HS [17]. Previous treatments were summarized in a variable called therapeutic burden, a measure already used in HS [18], which was calculated as the sum of all previous medical and surgical treatments before adalimumab start (this included any type of systemic medical treatment; in case of multiple cycles of the same antibiotic, they were counted only once-, and any surgical procedure).

Statistical Analysis

Univariable associations with the outcome (achieving HiSCR) were explored for all exposure variables, by means of chi-squared tests and logistic regression. Continuous variables were categorized where possible to illustrate these associations [19].

Table 1. Association between explanatory variables and HiSCR achievement among adolescent HS patients treated with adalimumab

Variable	Number (col. %)	HiSCR achieved at 6 months, Number (row %)	Odds ratio (95% CI)	p value ^a
Total	65 (100)	50 (76.9)	–	–
<i>Demographic and clinical characteristics (at adalimumab initiation)</i>				
Sex				
Female	44 (67.7)	34 (77.3)	1.06 (0.31–3.6)	0.92
Male	21 (32.3)	16 (76.2)	1	
Age at adalimumab start				
10–14.9 years	19 (29.2)	15 (79.0)	1.18 (0.32–4.3)	0.80
15–18.9 years	46 (70.8)	35 (76.1)	1	
Disease duration				
≤4 years	40 (61.5)	34 (85.0)	3.2 (0.97–10.5)	0.053
≥5 years	25 (38.4)	16 (64.0)	1	
Family history of HS				
Yes	25 (38.4)	19 (76.0)	0.92 (0.28–3.0)	0.89
No	40 (61.5)	31 (77.5)	1	
Smoking				
Yes	16 (24.6)	13 (81.3)	1.41 (0.34–5.8)	0.63
No	49 (75.4)	37 (75.6)	1	
Body mass index				
Underweight/healthy	29 (44.6)	20 (40.0)	1	0.17
Overweight/obese	36 (55.4)	30 (60.0)	2.25 (0.69–7.3)	
Hurley stage				
I	3 (4.6)	2 (66.7)	0.45 (0.04–5.5)	0.31
II	49 (75.4)	40 (81.6)	1	
III	13 (20.0)	8 (61.5)	0.36 (0.10–1.36)	
IHS4 at adalimumab start	12 (8–16)	–	–	–
Anatomical locations involved ^c				
Groin	47 (72.3)	34 (72.3)	0.33 (0.07–1.6)	0.17
Axillary	43 (66.2)	35 (81.4)	2.04 (0.63–6.7)	0.24
Gluteal	20 (30.8)	13 (65.0)	0.40 (0.12–1.33)	0.14
Inframammary	11 (16.9)	7 (63.4)	0.45 (0.11–1.8)	0.27
Genital	10 (15.4)	6 (60.0)	0.38 (0.09–1.56)	0.19
Facial	6 (9.2)	5 (83.3)	1.56 (0.17–14.5)	0.69
<i>Treatment-related characteristics</i>				
Previous medical treatments				
≤2	34 (52.3)	29 (85.3)	2.8 (0.8–9.3)	0.09
≥3	31 (47.7)	21 (67.7)	1	
Previous surgeries				
Yes	23 (35.4)	19 (82.6)	1.7 (0.47–6.1)	0.41
No	42 (64.6)	31 (73.8)	1	
Therapeutic burden				
≤3	40 (61.5)	34 (85.0)	1	0.053
≥4	25 (38.5)	16 (64.0)	0.31	
Biological drug started				
Adalimumab originator	42 (64.6)	34 (81.0)	1	0.30
Adalimumab biosimilar	23 (35.4)	16 (69.6)	0.54 (0.17–1.7)	
Initial dosage of adalimumab ^b				
80 mg EOW	32 (49.2)	28 (87.5)	7.0 (1.67–29.4)	0.018
40 mg EW	16 (24.6)	8 (50.0)	1	
40 mg EOW	17 (26.2)	14 (82.3)	4.7 (0.96–22.8)	
Dose change required: No	43 (66.2)	36 (83.7)	1	0.033
Yes, intensification	19 (29.2)	11 (57.9)	0.27 (0.08–0.90)	
Yes, de-intensification	3 (4.6)	3 (100)	–	

^ap value from logistic regression for the univariable association between exposure and HiSCR achievement. ^bEOW, every other week; EW, every week. ^cAssociations calculated for each anatomical location, as a binary variable (yes/no). IHS4 (International Hidradenitis Suppurativa Severity Score System) was not normally distributed and is summarized by median (p25–p75). –, Does not apply; HiSCR, Hidradenitis Suppurativa Clinical Response.

Results

A total of 65 patients from 9 HS units of six different Spanish regions (Madrid, Granada, Valencia, Barcelona, Alicante, and Balearic Islands) were included. Adolescents initiated adalimumab treatment between 2015 and 2023, with initiation years distributed as follows: 2015 (2), 2016 (2), 2017 (3), 2018 (8), 2019 (16), 2020 (8), 2021 (13), 2022 (10), 2023 (3). About two-thirds of patients were female. At adalimumab start, mean age was 15.5 years (sd = 2.0), mean BMI was 26.9 (sd = 6.3) and patients had a mean disease duration of 4.4 years (sd = 3.0). The prevailing starting dose was 80 mg EOW, which was seen in 32 patients (49.2%). Patients in the overweight or obese category were more likely to receive the adult dosage (40 mg EW or 80 mg EOW) than patients in the normal or underweight category (OR = 3.1, 95% CI = 0.97–9.7, p value = 0.052). Most frequent previous systemic treatments included oral clindamycin (57% of patients), doxycycline (55%) and isotretinoin (45%). Nineteen (29.2%) patients received rifampicin treatment, all of whom had also been treated with oral clindamycin; however, information regarding whether these treatments were administered simultaneously was unavailable. Demographic, clinical, and treatment-related characteristics are shown in Table 1.

Effectiveness

A total of 76.9% of adolescents achieved HiSCR at 6 months. A reduction in IHS 4 score was seen over the first 6 months, which generally was maintained during the first year (shown in Fig. 1). Nineteen patients required drug intensification: 7 of 48 (14.6%) patients who had been started on the adult dosage (80 mg EOW or 40 mg EW), and 12 of 17 patients (70.6%) who had been started on the adolescent dosage (40 mg EOW). The adolescent dosage was associated with a risk for needing intensification (OR = 14.1, 95% CI: 3.8–52.4, p value < 0.001), and this association was independent of age at adalimumab start, as the association persisted both in adolescents aged 15 and under, and above 15 years of age (p values: 0.012 and 0.006, respectively).

Total follow-up time on adalimumab treatment was 168.0 person-years. The median drug survival time for adalimumab was 5.6 years (25th percentile: 2.9 years). Seventeen patients (26.1%) required drug discontinuation, 12 (70.6%) of them due to ineffectiveness and 5 due to side effects, of whom 2 could later resume treatment. Three patients were de-intensified due to good disease control, all of them coming from the 80 mg EOW dosage.

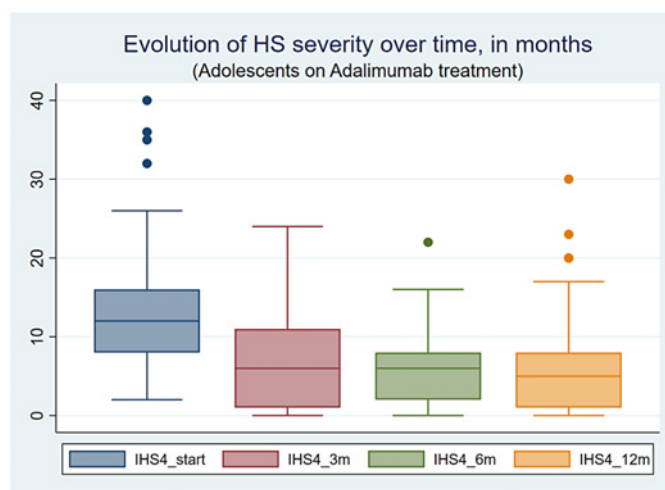


Fig. 1. Box plots showing the distribution of IHS4 scores at baseline, 3 months, 6 months, and 12 months of treatment with adalimumab in adolescents with hidradenitis suppurativa (HS). The y -axis represents IHS4, and the x -axis represents time in months. Each box displays the median and interquartile range (IQR), with whiskers extending to 1.5 times the IQR.

Safety

The total follow-up time for side effects was 186.8 person-years, as it included time until the last patient visit, regardless of whether adalimumab had been discontinued. Side effects were reported in 7 (10.8%) patients, of which 3 required drug discontinuation (4.6% of all patients). Five events occurred in patients that were on the 80 mg EOW dose, and two in patients on the 40 mg EOW dose. The most frequent side effect was respiratory tract infections, in 3 patients (2 of which discontinued treatment). Other reported side effects included paradoxical psoriasis in 1 patient (who required drug discontinuation), dizziness and nausea in another patient (who required a treatment pause but could restart it with good tolerability), local pain with injection in another patient (changed to another brand of adalimumab with good tolerability), and worsening of concurrent atopic dermatitis in another patient, the latter not requiring discontinuation. No side effects were reported in the 10–14 years age group (N = 12). All patients recovered. Another patient who discontinued adalimumab due to drug ineffectiveness was started on infliximab and developed leukocytoclastic vasculitis many weeks after infliximab initiation, which also resolved.

Discussion

We obtained promising effectiveness and safety data of adalimumab in adolescents with moderate-to-severe HS. Based on the long-term data from the open-label extension

of the PIONEER trials in adults, adalimumab may be more effective at younger ages than in adults, as 48.9% of patients had achieved HiSCR at 6 months in the extension, vs. 76.9% in this case series [20]. This could be due to adolescents in this series having less structural damage than adults from the PIONEER trials [7], or to differences in other baseline characteristics like a shorter disease duration or lower BMI in our series, among others, which might have influenced response. We did not find evidence that the adult dosage was more effective than the adolescent dosage to achieve HiSCR at 6 months, but reliable conclusions regarding potential differences in effectiveness of different dosages cannot be drawn, due to our limited sample size. However, the adolescent dosage (40 mg EOW) was strongly associated with a need for intensification in order to maintain response (OR = 14.1, 95% CI: 3.8–52.4, p value <0.001), suggesting the adult dosage (40 mg EW or the equivalent 80 mg EOW) might be a better option for disease control, also in adolescents. It is worth mentioning that 7 patients on the adult dosage required intensification to 80 mg EW to maintain response, which is an off-label dosage in this age group.

In terms of safety, the approved dosage for adults showed a similar safety profile than the approved dosage for adolescents, with 10.4% of patients showing an adverse event vs. 11.8%, respectively. Side effects were similar to those reported in the PIONEER trials [7], namely respiratory infections and a psoriasis-related event. Interestingly, only 4.6% of adolescents in this series required drug discontinuation due to side effects, compared to 15% of adult patients in the extension of the PIONEER trials [20], where mean patient-years of exposure was 2.2 years (vs. 2.6 years in this series).

Our study has important limitations, such as the absence of a comparator group in the assessment of effectiveness due to study design, its retrospective nature, and the relatively small sample size. Additionally, we lacked data on quality of life. However, the study also has many strengths, as it brings forward the longest multicentric case series to date of adolescents with moderate-to-severe HS treated with adalimumab, almost doubling the sample size of HS patients treated with biologics included in a recent systematic review [11]. In this review, 93.9% (31/33) of patients improved with several biologic treatments and varied regimes, however no effectiveness measurement could be specified. Our study in contrast provides measurements using validated scales used in HS evaluation such as HiSCR and IHS4, and a single biologic treatment (adalimumab), adding consistency to our results. Regarding effectiveness and safety data in this age group, our study is the only one to date to provide a long follow-up time in a real-world

setting, in contrast with data from case reports selected for the previously mentioned systematic review.

Adolescent patients suffering from HS may be particularly vulnerable in this impairing disease [10], as adolescence is already a challenging stage of life regarding mental health [21], and HS itself has been associated with increased anxiety, depression, and risk of suicidality [1]. Effective treatment should be initiated without delay to avoid structural damage and psychological impairment at an early age [4, 10]. However, pediatric patients have historically been excluded from HS clinical trials [22], leading to delays in acquiring evidence to support treatment initiation in this age group. An increasing amount of regulatory guidance and documentation advocate for the inclusion of children and adolescents in adult clinical research, including trials [23–25]. Until optimal evidence from these trials and large prospective registries [26] becomes available, our results support initiating adalimumab in adolescents with moderate-to-severe HS, with the possibility of using the adult dosage if needed for disease control.

Statement of Ethics

This study was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro (Comité de Ética de la Investigación del Hospital Universitario Puerta de Hierro Majadahonda); approval CEIm 70/23. Due to the study being retrospective and using de-identified data, the committee also granted an exemption from requiring patient written informed consent (CEIm 70/23).

Conflict of Interest Statement

Mercè Grau-Pérez has received financial support to attend conferences or seminars from Abbvie, Almirall, Janssen, Novartis, Pfizer, Sanofi and UCB. Cristina Ciudad has participated as principal investigator or sub-investigator in clinical trials, and/or has acted as an advisory board member and/or invited speaker for AbbVie, Almirall, Johnson and Johnson, Novartis and UCB. Alejandro Molina-Leyva reports consultancy/speaker's honoraria and/or travel grants and/or participated in clinical trials sponsored by AbbVie, Almirall, Boehringer Ingelheim, Celgene, Janssen Cilag, LEO Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, and UCB. Antonio Martorell has received honoraria and/or travel grants and/or has acted as an advisory board member for Novartis, AbbVie, Janssen Cilag, UCB, Lilly, LEO Pharma, L'Oreal, Sanofi, Boehringer Ingelheim, Almirall, Bristol Myers Squibb and Amgen. He has also worked as a principal investigator in clinical trials supported by AbbVie, UCB, Jansen, Bristol Myers Squibb, Lilly, Galderma, Sanofi, and Novartis. Eva Vilarrasa has participated as principal investigator or sub-investigator in clinical trials, and/or member of steering committees and/or advisor and/or invited speaker for AbbVie, Almirall, Amgen, Boehringer

Ingelheim, Biofrontera, Bristol Myers Squibb, Galderma, Isdin, Johnson & Johnson, Leo Pharma, Lilly, MSD, Novartis, Pfizer, Sandoz, Sanofi and UCB. Irene Albert: no conflicts of interest to declare. Juan Garcias-Ladaria has participated as principal investigator in clinical trials for Acelyrin, received financial support to attend conferences or seminars from Novartis and UCB and also received honoraria for advisory and as invited speaker from Novartis. Francisco Javier Melgosa received financial support to attend conferences or seminars from Abbvie, Almirall, Janssen, Novartis, Isdin, Sanofi, and UCB. Raquel Rivera has participated as principal investigator or sub-investigator in clinical trials, and/or member of steering committees and/or advisor and/or invited speaker for AbbVie, Boehringer Ingelheim, Johnson and Johnson, Novartis, and UCB. Minia Campos has received honoraria, travel grants or has acted as an advisory board member for Novartis, Pfizer, AbbVie, LEO Pharma, Sanofi, and Galderma. She has also worked as a principal investigator and sub-investigator in clinical trials supported by Sanofi, AbbVie, Pfizer, Galderma and Amgen. Sofia Haselgruber and Gemma Ochando: no conflicts of interest to declare. Jose Carlos Pascual received financial support to attend conferences or seminars from Abbvie, Janssen, Novartis, Sanofi and UCB. Also received honoraria for advisory from Abbvie, Novartis, and UCB. Ramón García-Ruiz has received financial support to attend conferences or seminars from Novartis. Fernando Alfageme received financial support to attend conferences or seminars from Abbvie, Almirall, Janssen, Novartis, and UCB.

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Author Contributions

Mercè Grau-Pérez: formal analysis, data curation, writing – original draft preparation, methodology (equal); Cristina Ciudad, Alejandro Molina-Leyva, Antonio Martorell, Eva Vilarrasa, Juan Garcias-Ladaria, Francisco Javier Melgosa, Raquel Rivera, Minia Campos, Sofia Haselgruber, Gemma Ochando, José Carlos Pascual, Ramón García-Ruiz, and Irene Albert: investigation (equal), writing – review and editing (equal); Fernando Alfageme: investigation (lead), conceptualization (lead), methodology (equal), writing – review and editing (lead), and supervision (lead).

Data Availability Statement

The data that support the findings of this study are not publicly available as they contain information that could compromise the privacy of research participants but are available from M.G.-P. upon reasonable request.

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