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E Vilarrasa has received consultancy/speaker's honoraria and/or travel support for attending meetings and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Meyers Squibb, Celgene, Gebro, Isdin, Janssen, LEO Pharma, Lilly, Merck Serono, MSD, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB.

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Abstract

Background and objectives

Survival analyses can provide valuable insights into effectiveness and safety as perceived by prescribers. Here, we aimed to evaluate adalimumab (ADA) survival and the interruption risk factors in a multicenter cohort of patients with hidradenitis suppurativa (HS). Moreover, we performed a subanalysis considering the periods before and after the onset of the COVID-19 pandemic.

Methods

We conducted a retrospective study including 539 adult patients with HS who received ADA from May 1, 2015, to December 31, 2022. Overall drug survival was analysed using Kaplan-Meier survival curves and compared between the subgroups via stratified log-rank test. Possible predictors for overall drug survival and reasons for discontinuation were assessed using univariate and multivariate Cox regression.

Results

Overall, 50.1% were females with a mean age of 43.5±1 years, and a mean BMI of 29.5±6.7. At the start of ADA, 95.29% were biologic-naïve and 24.63% had undergone surgical treatment. During follow-up, 9.46% of patients required dose escalation, while 39.92% interrupted ADA. Concomitant therapy was used in 64.89% of cases. A subanalyses comparing pre- and post-pandemic periods revealed a tendency to initiate ADA treatment at a younger age, among patient with higher BMI and at a lower HS stage after COVID-19 pandemic.

Interestingly, ADA demonstrated extended survival compared to previous studies, with a median overall drug survival of 56.2 months (95% CI 51.2 to 80.3). The primary causes for discontinuation were inefficacy (51.69%), followed by adverse effects (21.35%). Female sex, longer delay in HS diagnosis, higher baseline IHS4 score, and concomitant spondylarthritis were associated with poorer ADA survival or increased risk of discontinuation.

Conclusions

ADA demonstrated prolonged survival (median 56.2 months). While addition of antibiotics did not have a positive effect on survival rate, basal IHS4 proved useful in predicting ADA survival.

Introduction

Hidradenitis suppurativa (HS) is a persistent inflammatory cutaneous disease causing a high impact in quality of life[1,2], with an average delay of 10 years from firsts symptoms until diagnosis[3]. Treatment of HS is challenging due to the few approved medical options available[4]. Current treatment guidelines[5,6] recommend a combination of medical and surgical approaches, with antibiotics as the fist-line therapy and biological treatment as second-line option.

For a long period of time adalimumab (ADA) was the sole biologic agent approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for HS. This exclusivity prompted non-responsive patients to undergo intensified treatment regimens, combinations of therapies, exploration of off-label biological alternatives grounded in limited evidence, or enrolment in clinical trials. As a result, prolonged disparities in treatment access persisted among various geographical regions and hospitals. The advent of the COVID-19 pandemic further complicated patients' access to the dermatology department[7].

Significant progress has been made in HS medical research and clinical trials in recent years. The approval of secukinumab by EMA on June 13, 2023, following the SUNSHINE and SUNRISE trials[8], represents a substantial milestone. Furthermore, bimekizumab, another anti-IL17 agent, is expected to gain approval based on the outcomes of phase 2[9] and phase 3 BE HEARD I and II.

Drug survival studies are useful to understand the level of efficacy and safety perceived by prescribers in specific geographic, temporal, or therapeutic environments. However, they should not equate to efficacy or safety studies[10].

In fact, several biases such as heterogenicity in the interruption threshold, the influence of COVID-19 pandemic, and the absence of approved alternatives to ADA, need to be taken into consideration, among others.

The aim of the present study was to assess the survival of ADA in the daily clinical practice of a multicenter cohort of patients with HS from May 1, 2015, until December 31, 2022. Additionally, we conducted a retrospective analysis of potential demographic and clinical factors contributing to ADA survival and influencing dose escalation or discontinuation. To address the aforementioned biases, we assembled a large HS patient cohort undergoing ADA treatment with long-term follow-up. We further compared the results between pre- and post-pandemic periods to investigate possible differences in both groups.

Materials and Methods

Participants were identified through the electronic medical records of the dermatology department of 12 Hospitals in Spain. The inclusion criteria encompassed patients diagnosed with HS who received ADA treatment between May 1, 2015, and December 31, 2022. Patients who had received a different biologic treatment before ADA initiation were also included. We did not impose a minimum follow-up period, and only the first course of ADA was considered for analysis. Additionally, we did not differentiate between ADA and its biosimilar in our study. Consistent with prior regional studies[11], we conducted a sub-analysis comparing periods before and after the initiation of the COVID-19 pandemic in Spain. Considering that the pandemic context could have influenced treatment decisions for HS, we performed these temporal segmentation analyses to mitigate potential biases. Thus, we marked the end of

the pre-pandemic phase as of March 13, 2020, coinciding with the state of emergency declaration in our country. Strict lockdown measures were enforced until June 21, 2020, subsequently, the post-pandemic period extended from June 21, 2020, until December 31, 2022.The study received approval from the medical ethical committee of Hospital Parc Taulí under reference 2022/5109. Due to the retrospective nature of data collection from routine practice records, the committee granted an exemption for obtaining written consent for this study.

Patients' variables

Patient-related data encompassed various demographic outcomes including sex, age, body mass index (BMI), time to diagnosis, and smoking status. Baseline HS characteristics, such as Hurley stage, HS-Physician Global Assessment (HS-PGA), International Hidradenitis Suppurativa Severity Score System (IHS4), and Canoui-Poitrine phenotype, were also recorded. Additionally, comorbidities like dyslipidaemia, hypertension, type 2 diabetes mellitus, ischemic cardiopathy, hepatic failure, kidney failure, spondylarthritis, inflammatory bowel disease (IBD), mental disorders, and substance use disorder were considered.

Treatment variables

Treatment-related information consisted of previous treatments received, comprising topical antibiotics, doxycycline, rifampicin plus clindamycin, acitretin, isotretinoin, sulfone, biologic treatment, and previous surgical interventions including incision/drainage and steroid infiltration. Moreover, we identified cases where up-dosing, defined as any increase in the baseline dosage or a reduction in the interval between administrations, was necessary during follow-up. We

also documented the longest maintenance regimen observed throughout the follow-up period, ADA treatment interruption, HS-PGA, median IHS4 at the time of interruption, IHS4-55 achievement, as well as the reasons for discontinuation, inefficacy understood as either lack or loss of efficacy, adverse effects, loss of follow-up, poor adherence to ADA, and HS remission. We also recorded concomitant treatments added to ADA therapy and new treatments introduced after ADA discontinuation.

Statistical analysis

For statistical analysis, patient characteristics were described as mean (SD) or median (IQR), for continuous variables and as n (%) for categorical variables. Data were tested for normality and the appropriate parametric or non-parametric statistical test applied. Pearson's Chi square was used for categorical data. For numerical data, analysis of two groups was completed using an independent t-test or a non-parametric equivalent (Mann–Whitney test for unpaired and Wilcoxon test for paired samples). Overall drug survival was analysed using Kaplan-Meier survival curves and compared between the subgroups via stratified log-rank test. Separate survival curves were generated for discontinuation due to ineffectiveness and side-effects. Patients were censored when they were lost to follow-up, or when the biological agent was discontinued for reasons other than inefficacy, side-effects, or remission. Possible predictors for overall drug survival and reasons for discontinuation were assessed using univariate and multivariate Cox regression analysis. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using Rstudio 2023.03.0, R version 4.3.0 (2023-04-21 ucrt).

Results

Patients, comorbidities, and other treatments overall and by subgroups

A total of 539 patients were identified (Table 1 and 2). Overall, 50.1% of the patients were females, with a mean age at the start of ADA treatment being 43.5±1 years, and a mean BMI of 29.5±6.7 kg/m^2. The mean time from first symptoms until HS diagnosis was 10.2±11.6 years. In total, 87.82% of patients were either current or former smokers. Baseline HS characteristics revealed a predominance of Hurley II (40.81%) and III (56.36%) at the initiation of ADA treatment. Baseline HS-PGA showed a preponderance of HS-PGA 3 (34.19%), 4 (31.11%), and 5 (23.14%). IHS4 score at baseline was mild (3.51%), moderate (40.05%) and severe (56.44%). The Canoui-Poitrine et al. classification included LC1 (40.56%), LC2 (17.67%), and LC3 (41.77%).

The most prevalent comorbidities in our patient cohort were mental health disorders (29.81%), followed by cardiovascular risk factors such as dyslipidaemia (17.46%), hypertension (15.91%), and type 2 diabetes mellitus (10.78%). A significant number of patients received topical treatments (78.21%) and oral antibiotics such as doxycycline (66.23%) and a combination of rifampicin with clindamycin (64.57%) prior to ADA initiation. Overall, the majority of patients (95.29%) were biologic-naïve, and 24.63% had received surgical treatment at the time of starting ADA. Concomitant therapy to ADA was used in 64.89% of patients, with the majority receiving topical treatment (46.47%) or oral antibiotics (32.12%).

During treatment, 9.46% of patients required ADA up-dosing. The most commonly observed maintenance regimens during follow-up were 80 mg every

2 weeks (52.58%), 40 mg weekly (38.2%), and 80 mg weekly (7.51%). In total, 39.92% of patients interrupted ADA therapy at some point during the follow-up period. At the time of ADA interruption, the predominant HS-PGA score was 3 (33.79%), with a median IHS4 score of 5 (IQR 1-18.5). The primary reasons for ADA discontinuation, as determined by the prescribers, were inefficacy (51.69%) followed by adverse effects (21.35%) such as local reaction post-injection, headache or paradoxical reaction.

Following ADA discontinuation, a review of new biological treatments revealed that IFX was overall the most commonly prescribed (27.56%), followed by secukinumab (23.23%). Considering the baseline characteristics of the group of patients receiving an anti-IL17 agent after ADA interruption, 63.2% were females, with a median BMI of 28.6 (IQR 26.43-34.78) and a moderate to severe IHS4 (56.52% and 39.13%, respectively). Interestingly, 2 (5.3%) of them presented a concomitant spondyloarthritis.

Subanalyses, as presented in Table 1 and 2, revealed few statistically significant differences when comparing the pre-pandemic and post-pandemic periods described as follows. After the pandemic, there was a notable rise in the mean BMI (p=0.005). Conversely, the mean age at the initiation of ADA treatment (p=0.003) and severity scores, including Hurley stage (p=0.003), HS-PGA (p=0.043), and IHS4 (p=0.035), demonstrated a significant decrease in the group of severe patients. Additionally, a higher frequency of patients requiring ADA up-dosing (p=0.001) or interrupting ADA therapy (p=0.002) was noted in the pre-pandemic period. As anticipated, concomitant oral antibiotic usage also displayed a higher occurrence during the same period (p=0.004).

Regarding biological treatments, we observed a significant reduction in IFX prescription (p=0.043) and an increase in secukinumab usage during the post-pandemic period (p=0.001).

Factors contributing to the risk of ADA up-dosing or discontinuation

Our analyses of factors contributing to the risk of ADA up-dosing revealed that a basal HS-PGA score of 2 (OR 2.51, 95% CI 1.04 to 5.59; p=0.036, reference HS-PGA 1) was a significant factor. In the study of risk factors contributing to ADA discontinuation, we found a higher probability in females (OR 1.47, 95% CI 1.03 to 2.1; p=0.038) with a longer delay in HS diagnosis (OR 1.03, 95% CI 1.01 to 1.05; p=0.012), those with concomitant inflammatory bowel disease (OR 2.83, 95% CI 1.04 to 8.5; p=0.043) and with a worse basal stage: Hurley III (OR 1.87, 95% CI 1.29 to 2.72; p=0.001, reference Hurley I), HS-PGA 5 at baseline (OR 1.7, 95% CI 1.06 to 2.74; p=0.029, reference HS-PGA 2) and severe IHS4 (OR 1.73, 95% CI 1.16 to 2.59; p=0.009, reference mild IHS4).

ADA survival and associated factors

Median overall drug survival (Fig. 1) was calculated as 56.2 months (95% CI 51.15 to 80.25). The survival rates for ADA at 12, 24, 36, and 48 months were 82.95%, 71.68%, 64.42%, and 58.09%, respectively. During the pre-pandemic period, the median drug survival was 51.65 months (95% CI 37.68 to 52.11), and ADA survival rates at 12, 24, 36, and 48 months were 84.23%, 70.13%, 59.87%, and 51.39%, respectively. Median drug survival was not reached at the end of the post-pandemic period; however, ADA survival rates at 12 and 24 months were 82.12% and 68.42%, respectively. Log-rank p-value between pre- and post-pandemic was 0.87.

Fig. 2 and Fig. 3 display overall stratified survival curves for inefficacy (lack or loss of efficacy) and adverse effects, respectively. No statistically significant differences in terms of survival rate were observed for patients receiving concomitant antibiotics or previous biological treatments.

Considering the entire study period, a worse IHS4 score at baseline (HR 1.018, 95% CI 1.01 to 1.03; p=0.01) and previous treatment with sulfone (HR 2.25, 95% CI 1.13 to 4.46; p=0.02) were significantly associated with shorter drug survival in the univariate Cox Regression analyses. During the post-pandemic period, female sex (HR 2.03, 95% CI 1.01 to 3.78; p=0.03), a previous diagnosis of IBD (HR 3.42, 95% CI 1.22 to 9.62; p=0.02) and history of other biological treatment before ADA (HR 3.26, 95% CI 1.01 to 10.61; p=0.05) were associated with shorter survival time. The presence of other comorbidities or medications before ADA initiation was not significantly associated with ADA survival.

In the multivariate Cox regression analysis of the whole period female sex (HR 2.92, 95% CI 1.61 to 5.3; p=0.001), younger age (HR 1.03, 95% CI 0.95 to 1; p=0.037), current (HR 2.46, 95% CI 1.16 to 5.2; p=0.02) or former smoking status (HR 3.84, 95% CI 1.43 to 10.3; p=0.007), spondylarthritis diagnosis (HR 1.95, 95% CI 1.01 to 3.8; p=0.047) and prior treatment with sulfone (HR 2.12, 95% CI 1.05 to 4.3; p=0.035) were identified as factors significantly associated with worse drug survival. During the post-pandemic, also previous receipt of rifampicin and clindamycin (HR 0.45, 95% CI 0.239 to 0.86; p=0.016) and prior biologic treatment before ADA (HR 4.03, 95% CI 1.18 to 13.79; p=0.026) contributed to a worse drug survival.

Discussion

As it is widely recognized, clinical trials often underestimate the true clinical response to treatments observed in real-world clinical practice. The 3-year open-label extension (OLE) PIONEER I and II trials reported a response rate of 52.3% up to week 168 using last observation carried forward analysis[12,13], underscoring the importance of real-world evidence to complement existing knowledge[14]. In this context, survival analyses can provide valuable insights into the use of ADA in specific geographic and temporal settings, but their results must be interpreted cautiously. In this study, we assessed the survival of ADA in the daily practice of a multicentric cohort of patients with HS (N=539) and retrospectively reviewed factors contributing to ADA survival and discontinuation.

Previous survival studies for ADA in HS, such as the one conducted by Ring et al.[15] examined ADA survival in 241 HS patients from January 1st, 2005, to December 31st, 2018, reporting a median overall drug survival of 8.28 (IQR 5.04 to 14.50) months. Consistent with our results, this study found that female sex was associated with reduced drug survival, but no other factors significantly influenced ADA survival. On the other hand, Prens et al.[16] evaluated ADA survival in 104 HS patients from January 2008 to June 2020, reporting a median overall drug survival for ADA of 18.10 months (95% CI 11.4 to 24.8) and drug survival rates of 56.3% (12 months) and 30.5% (24 months). Their study revealed that older age at the start of treatment, longer disease duration, more severe disease, and a higher BMI were associated with long-term ADA survival.

In our cohort, eligible patients for ADA had moderate to severe HS with a mean time from first symptoms until HS diagnosis of 10 years. Most of them had received topical or oral antibiotics but were biologic therapy-naïve before starting ADA. Notably, a significant proportion of patients interrupted ADA therapy (39.92%) with a median IHS4 score of 5, though, only a small percentage of patients (9.46%) required up-dosing during follow-up. Consistent with other studies[16], the main reasons for ADA interruption were inefficacy (51,69%) and adverse effects (21.35%).

The subanalyses comparing pre- and post-pandemic periods revealed a tendency to initiate ADA treatment at a younger age, among patient with higher BMI and at a lower HS stage after COVID-19 pandemic. Additionally, we observed a higher rate of patients requiring ADA up-dosing, interruption, or concomitant oral antibiotics before the pandemic. Moreover, secukinumab became the most prescribed alternative (40%) after ADA interruption in the post-pandemic, suggesting anti-IL17 therapies as current options for patients non-responsive to ADA[17,18]. Conversely, the utilization of IFX notably declined, likely attributable to the prioritization of non-hospitalization treatments following the pandemic.

Analyses of the factors contributing to the risk of ADA up-dosing identified a baseline HS-PGA score of 2 as a predictor. However, it is crucial to approach this finding with caution, as categorized IHS4 and Hurley scores did not corroborate the aforementioned results. Additionally, female sex, an extended delay in HS diagnosis, concurrent IBD and the presence of severe basal disease were associated with a higher risk of ADA interruption, consistent with other studies[15,16].

Regarding our survival rates, they were notably longer compared to previous studies. We hypothesize that this difference may be attributed to various factors including differences in the periods of time assessed and specific geopolitical variations between countries or regions. In Spain, in line with current European Guidelines for HS, there is a lack of a therapeutic protocol in cases of ADA failure. Additionally, since all biological treatments are fully funded by the National Health System after authorization, patients may have continued ADA treatment for longer compared to countries with different financial systems. Furthermore, the absence of approved alternatives for HS might explain the extended duration of ADA. Lastly, the notable factors emphasized in our study included a high proportion of concomitant medication involving topical or oral antibiotics, as well as the option to up-dose during follow-up.

In the context of the regression analysis, our findings reveal that female sex, younger age, a higher IHS4 score at baseline, current or former smoker status, concomitant spondylarthritis, and prior treatment with sulfone were significantly associated with a poorer ADA survival throughout the entire study period. Furthermore, in the post-pandemic period, factors such as female sex, a history of previous biological treatment before ADA, and a diagnosis of IBD were linked to worse survival. Therefore, it is plausible to hypothesize that the presence of concomitant immune-mediated inflammatory diseases, such as spondyloarthritis and IBD, may contribute to a diminished ADA survival, potentially due to an increased disease burden[19]. Finally, in contrast to other studies[16], it is noteworthy that BMI did not exert any influence, either in the overall analysis or in the subanalysis of this present study.

The study has some limitations, including its retrospective design and the inclusion of a sample of patients from a single country. Additionally, we did not distinguish between adalimumab and biosimilar, which might have impacted our results[20]. Nevertheless, Grau-Pérez et al.[21] did not observe differences in ADA survival between the two groups after following 84 patients with HS from 2016 until 2021.

In conclusion, the present study revealed a median overall drug survival of 56 months in HS patients treated with ADA. It is remarkable that, while addition of antibiotics did not have a positive effect on survival rate, basal IHS4 proved useful in predicting ADA survival. As we look ahead, we anticipate significant advancements in HS management in the coming years. We hope that future evidence and guidelines will soon provide new medical strategies for patients with moderate and severe HS.

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Table 1. Patients' and treatment medical history (overall and pre-/post-pandemic subgroups).

Table 2. Adalimumab regimen, discontinuation, and new treatments after discontinuation.

Fig. 1. Adalimumab survival overall period (a), during pre-pandemic (b) and thorough post-pandemic (c)

Fig. 2. Overall stratified survival for inefficacy (lack or loss of efficacy).

Fig. 3. Overall stratified survival for adverse effects.