ORIGINAL ARTICLE

Real-world effectiveness of adalimumab in patients with moderate-to-severe hidradenitis suppurativa: the 1-year SOLACE study

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Abstract

Background Long-term, real-word data are needed to help manage patients with hidradenitis suppurativa (HS) through this recurrent, painful and debilitating disease.

Objectives To primarily measure real-world effectiveness of adalimumab in HS and to secondarily observe clinical course of HS in the light of patients' response.

Methods In SOLACE, adults with moderate-to-severe HS in need for change in ongoing therapy were treated with adalimumab for up to 52 weeks as per physician's medical practice. Treatment effectiveness was measured by Hidradenitis Suppurativa Clinical Response (HiSCR). Inflammatory nodules, abscesses and draining fistulas were counted, Hurley stage was assessed, and disease severity was rated using the International HS Severity Scoring System (IHS4). A post hoc analysis further explored the HiSCR response by abscess and inflammatory nodule (AN) count at baseline (low, medium and high) and gender. Spontaneously reported safety events were collected.

Results From 23 Canadian centres, 69% of the 138 patients achieved HiSCR at week 24, which increased to 82% and 75% at week 52 in patients with medium and high AN counts, respectively. Gender (4 times the odds for female) and age at HS onset (5% decrease with each additional year) had an effect on achieving HiSCR. Treatment with adalimumab led to an important decrease in number of lesions in responders, with most gains observed in inflammatory nodules, more frequently in the lower body area of patients in the high AN count group. The IHS4 scores of responders were substantially lowered, with a larger decrease in patients of the high AN count group. No new safety signal was detected.

Conclusions The effectiveness of adalimumab was maintained during this 1-year period, and an optimal gain was documented for patients with medium and high AN counts. These real-world data support a prompt treatment of HS patients and the use of IHS4 to monitor treatment.

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Conflict of interest

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Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory and debilitating skin disease characterized by recurrent painful nodules, abscesses and draining sinus tracts primarily in intertriginous areas.[1] In a recent review, the prevalence of HS in the general US and European populations was summarized to be between 0.7% and 1.2%.[2]

Adalimumab (Humira®; AbbVie Inc., North Chicago, IL, USA) is currently the only approved drug to treat moderate-to-severe HS, based on the two phase-3 PIONEER studies.[3] Administered at a weekly dose of 40 mg after a loading dose, adalimumab is an effective and safe therapeutic option for medium- and long-term control of moderate-to-severe HS.[4,5]

Currently, there is a need for long-term, real-world data on the effectiveness of adalimumab for the treatment of moderate-to-severe HS patients,[6,7] as less controlled settings in real-world populations may impact effectiveness responses, thus patient management. There is also a need to observe effectiveness in the light of changes in secondary outcomes on clinical course of HS, such as the International HS Severity Scoring System (IHS4).[8] The primary objective of SOLACE was to assess adalimumab real-world effectiveness, using the Hidradenitis Suppurativa Clinical Response (HiSCR),[9] in moderate-to-severe HS over a 1-year period. The study also aimed at describing variations in the clinical course of HS, at identifying prognostic factors and, through a post hoc analysis, at exploring response data by abscess and inflammatory nodule (AN) count at baseline (low, medium and high) and by gender.

Materials and Methods

Study design and patients

In SOLACE – a 1-year prospective, observational, multicentre Canadian postmarketing study – adult patients (≥18 years) with a clinical diagnosis of moderate-to-severe HS were enrolled if they were in need for change in ongoing therapy for any reason including, but not limited to, inadequate response, intolerance, suboptimal compliance or patient preference. Written informed consent was obtained from each patient prior to data collection.

Patients were excluded if they were participating in a clinical interventional study, had been treated with adalimumab or any other biologic agents for HS prior to baseline visit, or had any other active skin disease or condition that prohibited the patients from participating in the study or obscured the assessment of the treatment of HS.

Treatment and assessments

Patients were treated with adalimumab and followed for up to 52 weeks in 23 Canadian centres (Table S1), in accordance with the physician's usual medical practice and as per regional requirements. Study assessments were performed during patients' routine care visits, at approximately 12, 24, 36 and 52 weeks after baseline.

Treatment effectiveness was measured by HiSCR, defined as a 50% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline.[9,10] The HS lesions were counted, specified by body areas and classified as abscess, inflammatory nodule and draining fistula.[11] The Hurley stage was assessed,[12] and HS severity was estimated using the IHS4.[6] The number of HS flares, defined as at least 25% increase in AN counts with a minimum increase of 2 relative to baseline, and the number of days on flare were also collected.

Safety assessments included spontaneously reported serious adverse events (AEs), non-serious event of malignancy in patients 30 years of age and younger,[13] unusual failure in efficacy and AEs leading to discontinuation. These were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Statistical analysis

Continuous data were summarized via PROC MEANS – mean, standard deviation (SD), median and range – and categorical data were presented as counts and percentages via PROC FREQ, presented with a 95% confidence interval (CI). The 95% CI was estimated using Wald asymptotic confidence limits based on the normal approximation to the binomial distribution. All missing data, except for the sensitivity analysis of the primary outcome, were not imputed. Missing data were considered missing at random.

For the primary endpoint – the proportion of patients achieving HiSCR at week 24 – all patients were included in the analysis as no patient changed treatment prior to week 24. To assess the

impact of missing data on the primary endpoint estimate, a sensitivity analysis was performed using two imputation methods: (a) non-responder imputation (NRI); that is, patients who did not provide week 24 efficacy data or dropped out of the study prior to week 24 were considered as non-responders; and (b) last observation carried forward (LOCF); that is, the last efficacy assessment prior to week 24 was used for those with missing week 24 assessment.

A logistic regression analysis was conducted to examine the effect of potential prognostic factors on the response at week 24. These were as follows: age, gender, age at HS onset, number of affected body areas at baseline, surgical procedures, disease-related events, family history of HS, smoking status at baseline, Hurley worst stage (HWS) at baseline, topical route of administration, intralesional steroid injection, systemic route of administration and geographic region.

To gain additional insights on treatment effectiveness, clinical course of HS and reported safety data, a post hoc analysis was conducted observing response data by AN count at baseline, that is ≤5, low; 6-10, medium; and ≥11, high, and by gender for the 24-week responders/non-responders. Responders were defined as those meeting the definition of HiSCR responders at week 24. All calculations and analyses were performed using SAS version 9.4 (Cary, NC, USA: SAS Institute Inc.).

Results

Patient characteristics

A total of 165 patients from 23 Canadian centres participated in the study, with 138 and 155 included in the intent-to-treat population and the safety population, respectively (Fig. 1). Mean ± SD age was 37.8 ± 12.2 years, and mean ± SD age at HS onset was 22.8 ± 11.1 years (Table 1). The majority was White (82.6%) and female (75.4%). At baseline, the HS status of most patients was assessed as Hurley stage II (68.8%) and as severe (70.3%) based on IHS4 scoring. One hundred and twenty (72.7%) patients completed the study (Fig. 1).

Patients achieving HiSCR

A proportion of 68.9% (95% CI: 60.6%, 77.2%) of patients achieved HiSCR at week 24 – study primary endpoint – which was maintained at week 52 (Fig. 2a and Table S2). The proportion of patients with severe HS who achieved HiSCR increased slightly from week 24 (69.9%) to week 52 (75.9%; Fig. 2b). Observed by AN count at baseline, the proportion of responders was higher in patients with medium and high counts than with a low count, which was to be expected as HiSCR is related to the decrease in AN counts (Fig. 2c). At week 52, the proportions of patients with medium and high AN counts who achieved HiSCR were 82.4% and 75.0%, respectively.

HS lesions

From baseline, the mean AN count decreased by 8.4 at week 24 and by 9.5 at week 52, with the declining number of inflammatory nodules contributing more to the decrease in AN count than the declining number of abscesses (Table S3). The most affected body areas were the axilla (73.7%–76.0% of patients) and groin (65.4%–71.2%; Fig. S1). The proportion of patients who experienced flare during the study was between 3.3% and 6.7%, and the median (range) duration of flares was 36.0 (1–359) days (Table S4).

The post hoc analysis shows that the 24-week responders (Fig. 3a) had a more important decrease in lesion counts than non-responders (Fig. S2). The most gains were observed in

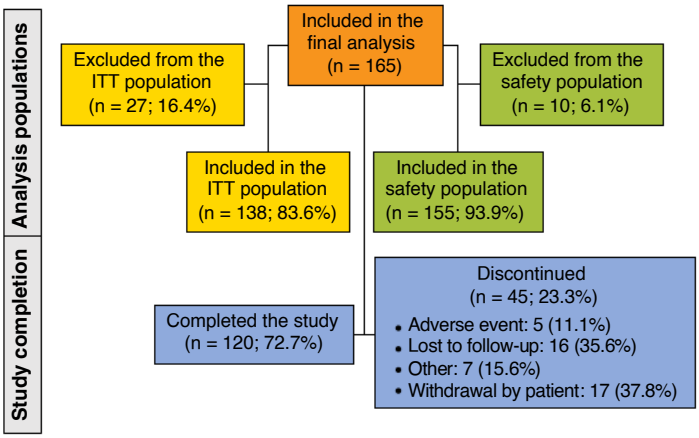

Figure 1 Patient flow diagram for the SOLACE study. ITT population: patients who took at least one dose of adalimumab and provided at least one postbaseline assessment; safety population: patients who took at least one dose of adalimumab. ITT: intent to treat.

Table 1 Patient demographics and baseline characteristics, ITT population

Characteristic	Mean (SD) or *N* (%)
Age (years)	37.8 (12.2)
Gender	
Female	104 (75.4%)
Male	34 (24.6%)
Race	
American Indian or Alaska Native	8 (5.8)
Asian	12 (8.7)
Black or African American	3 (2.2)
Multiple	1 (0.7)
White	114 (82.6)
BMI (kg/m^2)	36.8 (7.8)
Weight (kg)	104.3 (24.3)
Cigarette user†	74 (47.7)
Alcohol user†	116 (74.8)
Age at HS onset (years)	22.8 (11.1)
Years since HS onset (years)	14.9 (11.7)
Years since HS confirmed diagnosis (years)	3.4 (5.5)
Family history of HS	66 (42.6)
Lesion counts	
Abscesses	3.2 (4.8)
Inflammatory nodules	10.1 (11.3)
Draining fistulas	3.8 (6.5)
AN	13.3 (13.6)
HWS	
I	5 (3.6)
II	95 (68.8)
III	38 (27.5)
IHS4 scoring	
Mild	7 (5.1)
Moderate	34 (24.6)
Severe	97 (70.3)
Disease-related comorbidities reported by ≥10% of patients†	
Obesity	75 (59.1)
Depression	39 (30.7)
Irregular menstrual cycles	30 (23.6)
PCOS	23 (18.1)
Type 2 diabetes mellitus	23 (18.1)
Hypertension	22 (17.3)
Psoriasis	18 (14.2)
Pilonidal cyst	15 (11.8)
Contracture/strictures due to HS scarring	13 (10.2)

All data are mean ± SD unless otherwise stated.
AN, abscesses and inflammatory nodules; BMI, body mass index; HS, hidradenitis suppurativa; HWS, Hurley worst stage; IHS4, International Hidradenitis Suppurativa Severity Score System; ITT, intent to treat; PCOS, polycystic ovary syndrome; SD, standard deviation.
†Provided for the safety population (*N* = 155)

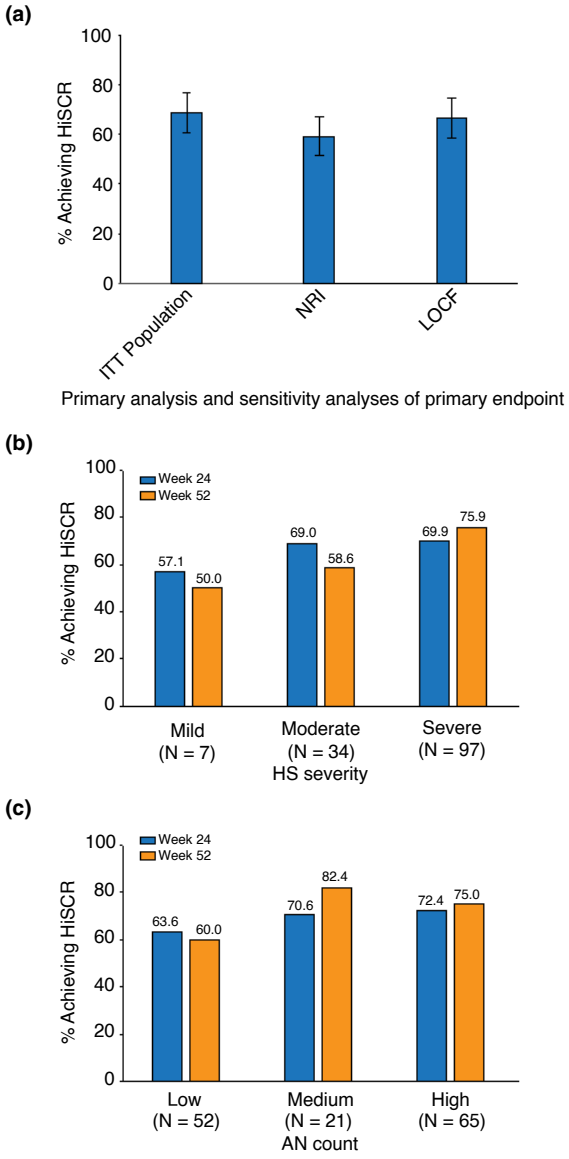

Figure 2 Proportion (%) of patients achieving HiSCR, achieved if there was at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count relative to baseline. (a) By primary analysis (ITT population) and sensitivity analyses (NRI and LOCF) of the primary endpoint, that is at week 24. Bars show confidence intervals. (b) By HS disease severity based on IHS4 points: ≤3 – mild; 4–10 – moderate; and ≥11 – severe, at weeks 24 and 52. (c) By AN count at baseline: ≤5 – low; 6-10 – medium; and ≥11 – high, at weeks 24 and 52. AN, abscesses and inflammatory nodule; HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4, International Hidradenitis Suppurativa Severity Score System; LOCF, last observation carried forward; NRI, non-responder imputation; ITT, intent to treat.

inflammatory nodules, especially for the lower body area in the high AN count group (mean ± SD at baseline = 10.8 ± 6.0; week 24 = 2.0 ± 2.3; week 52 = 1.7 ± 2.3; Fig. 3a). By gender, lesion counts tended to be higher in males' lower body area than females', while the counts were more mixed between genders for the upper body area (Fig. 3b).

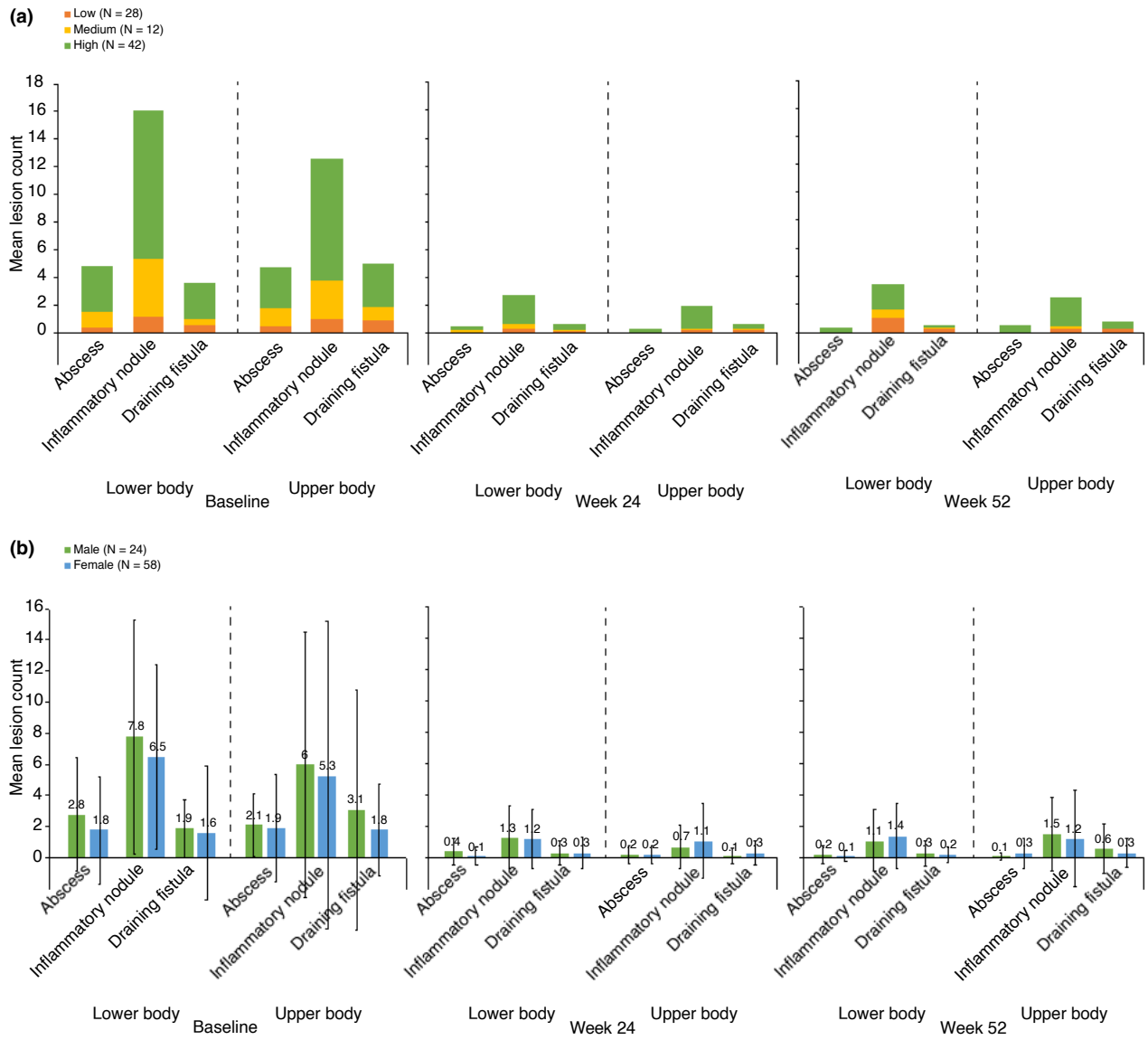

Figure 3 Mean number of abscesses, inflammatory nodules and draining fistulas counted on the lower and upper body areas of the week 24 responders, at baseline, week 24 and week 52. Responders were defined as those with a 50% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline, which excluded partial responders, that is those with a 25% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline. Lower body area includes abdomen, groin, things, pubic, genital, perineal, perianal and buttock. Upper body area includes mammary and axilla. (a) By AN count at baseline: ≤5 – low; 6-10 – medium; and ≥11 – high. (b) By gender. Bars show SD. AN, abscesses and inflammatory nodule; SD, standard deviation.

HS severity

Treatment with adalimumab led to an important decrease in IHS4 scores in responders from baseline to week 24 and to week 52 for all AN count groups. The larger decrease was measured in the high AN count group (24-week responders: mean IHS4 ± SD at baseline = 54.1 ± 47.5, week 24 = 7.9 ± 9.3 and week 52 = 8.8 ± 9.7; and 24-week non-responders: mean IHS4 ± SD at baseline = 43.8 ± 29.6, week 24 = 42.0 ± 36.2 and week 52 = 27.3 ± 30.2; Fig. 4a and Fig. S3a).

The number of patients with severe HS decreased from 8 patients in the low and medium AN count groups at baseline to none at weeks 24 and 52, whereas in the high AN count group,

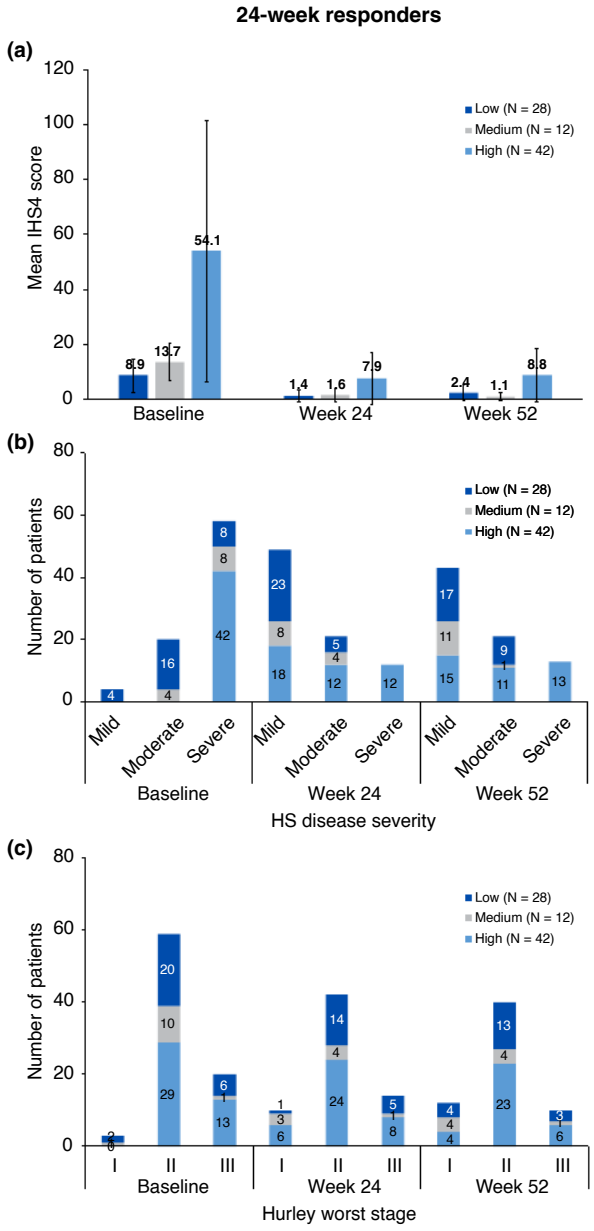

Figure 4 IHS4 scores, HS disease severity and HWS by baseline AN count in 24-week responders at baseline, week 24 and week 52. Responders were defined as those with a 50% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline, which excluded partial responders, that is those with a 25% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline. (a) Mean IHS4 score = (number of nodules*1) + (number of abscesses*2) + (number of draining fistulas (fistulas/sinuses)*4). Bars show SD. (b) Number of patients by HS disease severity, based on IHS4 points: ≤3 – mild; 4-10 – moderate; ≥11 – severe. (c) Number of patients by HWS. AN, abscess and inflammatory nodule; HS, hidradenitis suppurativa; HWS, Hurley worst stage; IHS4, International Hidradenitis Suppurativa Severity Score System; SD, standard deviation.

patient number decreased from 42 at baseline to 12 and 13 at weeks 24 and 52, respectively. Minimal changes in HS severity were observed in the 24-week non-responders (Fig. S3b). Due to the efficiency of treatment in patients with moderate-to-severe HS, in the 24-week responders the number of patients with mild HS increased from 4 (all with a low AN count) at baseline to 49 (23, 8 and 18 patients with low, medium and high AN counts, respectively) at week 24, which was similar at week 52 (Fig. 4b).

In 24-week responders (Fig. 4c), the number of patients with HWS II and HWS III was numerically lower over time in the medium and high AN count groups, respectively. Changes in HWS were small among the non-responders (Fig. S3c).

Prognostic factors

Proportionally, more males than females were responders (males 82.8% and females 64.4%) compared with non-responders (males 17.2% and females 35.6%) (Table S5). A logistic regression analysis confirmed that male responders have a significantly higher probability, approximately 4 times the odds of female responders, of achieving HiSCR at week 24 (odds ratio = 0.242; 95% CI: 0.074, 0.791; $P = 0.0189$). A comparison of the age at HS onset indicated that the odds of a clinical response at week 24 decreased by 5% with each additional year (odds ratio = 0.954; 95% CI: 0.914, 0.995; $P = 0.0278$).

Safety

A proportion of 12.9% reported at least one treatment-emergent AE (TEAE; Table 2). More female responders (14.2%) reported TEAEs than male responders (9.5%), and the number of events was proportionally greater in female responders (41 in females and 7 in males). Three (1.9%) patients reported serious and severe TEAEs assessed as reasonably possibly related to adalimumab: myelitis, which led to treatment discontinuation in 1 (0.6%) female; a soft tissue infection in 1 (0.6%) female; and an anal abscess in 1 (0.6%) male patient. One female patient (0.6%) was discontinued from treatment due to 3 severe TEAEs (arthritis, depression and urticaria), which were assessed as reasonably possibly related to adalimumab. Neither death nor malignancy in patients ≤ 30 years of age was reported during the study. No new safety signals related to adalimumab were observed.

Discussion

The HiSCR is recognized as the gold standard primary outcome in HS clinical trials[2,9,10] and has been included in patient management guidelines.[14,15] The response measured in SOLACE is slightly higher than the response observed in the PIONEER I and II studies at week 12 (60.0% in SOLACE and 50.6% in pooled data from the PIONEER I and II studies),[4] and in the long-term, pooled data of PIONEER I, PIONEER II and the open-label extension (OLE) at weeks 24 and 36.[4] It is also higher than reported in a recent real-world study, including 389 HS patients treated with adalimumab from 21 Italian centres at

Table 2 Overview of safety events reported during the SOLACE study, safety population

	Males *n* (%)		Females *n* (%)		ITT population *n* (%)	
	Patients (*N* = 42)	Events (*N* = 7)	Patients (*N* = 113)	Events (*N* = 41)	Subjects (*N* = 155)	Events (*N* = 48)
All reported TEAEs	4 (9.5%)	7 (100.0%)	16 (14.2)	41 (100.0)	20 (12.9)	48 (100.0)
Severe TEAEs	3 (7.1%)	4 (57.1)	6 (5.3)	8 (19.5)	9 (5.8)	12 (25.0)
TEAEs related to study drug	2 (4.8)	2 (28.6)	9 (8.0)	24 (58.5)	11 (7.1)	26 (54.2)
Serious TEAEs	3 (7.1)	4 (57.1)	6 (5.3)	7 (17.1)	9 (5.8)	11 (22.9)
TEAEs with fatal outcome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to treatment discontinuation	1 (2.4)	1 (14.3)	4 (3.5)	15 (36.6)	5 (3.2)	16 (33.3)
Malignancies in patients ≤30 years of age	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs reported by ≥1% ITT population						
Injection site pain	0 (0.0)	0 (0.0)	2 (1.8)	3 (7.3)	2 (1.3)	3 (6.3)
Pain in extremity	1 (2.4)	1 (14.3)	1 (0.9)	1 (2.4)	2 (1.3)	2 (4.2)
Depression	0 (0.0)	0 (0.0)	2 (1.8)	2 (4.9)	2 (1.3)	2 (4.2)
Psoriasis	0 (0.0)	0 (0.0)	2 (1.8)	2 (4.9)	2 (1.3)	2 (4.2)
Treatment exposure (days), median (range)						
Time in trial	365.0 (33–531)					
Treatment duration	349.0 (1–456)					

ITT, intent to treat; TEAE, treatment-emergent adverse event.

week 52 (HiSCR responders: 70.5% in SOLACE and 53.9% in the real-world Italian study).[7]

The SOLACE real-world population differs from the PIONEER clinical trial populations, explained in part the different treatment efficacy/effectiveness, hence supporting the pertinence of gathering long-term, real-world data. As such at baseline, 15%–20% more patients assessed Hurley stage II in SOLACE than in PIONEER I and II, and inversely, less patients assessed Hurley stage III.[16]

The post hoc analysis showed that highly inflammatory patients with severe HS (IHS4 ≥ 11 points) and those with medium (6–10 lesions) and high (≥11 lesions) AN counts at baseline benefited the most from the treatment, leading to a HiSCR of ≥75% at week 52. The regression analysis showed that male responders were more likely to achieve HiSCR at week 24 than female responders (by fourfold) and that the younger a patient experienced HS onset, the more effective a treatment with adalimumab will be (HiSCR at week 24 decreases by 5% with each additional year of HS onset). In a post hoc analysis reported by Frew *et al.*,[17] it was found that draining tunnels, smoking, antibiotics and BMI influenced HiSCR response in the PIONEER II study; however, that gender had no influence on HiSCR achievers ($P = 0.70$).

Our data on treatment effectiveness versus age at HS onset add to findings recently reported by Marzano et al.[7] on the evidence of a 'window of opportunity' in the treatment of HS patients with adalimumab (odds ratio = 1.92 for therapeutic delay ≥10 years; 95% CI: 1.28, 2.89; $P = 0.0016$). A challenge remains as HS patients may experience an average delay of 7–10 years between disease onset and diagnosis.[18,19]

Patients in the SOLACE study had a greater decrease in AN count than those treated with adalimumab in the PIONEER I and II studies at week 12 (mean change: −8.4 in SOLACE and −5.47 and −5.64 in PIONEER I and II studies, respectively),[17] and those treated with adalimumab in PIONEER I and II studies pooled with the OLE study at weeks 24 and 36.[4] Similar to results reported from these studies, a greater improvement was observed in inflammatory nodules than in draining fistulas and abscesses during the SOLACE study.[4]

Our results show that in adalimumab responders, lesion counts decreased from baseline to weeks 24 and 52 in both the lower and upper body areas, in all AN count groups. In 24-week responders, the main observations were as follows: (a) a decrease between 83% and 100% in number of abscesses, (b) proportionally, a slightly larger decrease in lesion counts located in the upper body area of patients in the medium AN count group (96% at week 24 and 93% at week 52) than in the low and high AN count groups, and for lesions located in lower body area (75%–90%, except for 17% observed in the low AN count group in the lower body area), and (c) a decrease between 75% and 100% in the number of draining fistulas (except for the low AN count group in the lower body area; 67%).

Whereas the Hurley clinical grading system is commonly used for screening and grading severity of HS,[2] the IHS4 – recognized as simple to use and adapted for clinical research and daily practice[6] – has been validated and reported in several clinical studies for assessing HS response.[8,17,20-23] To our knowledge, SOLACE is the first study reporting changes in IHS4 scores observed by baseline AN count.

Our results corroborate the validity of using IHS4 for collecting real-world data, as the change in scores varied consequently with responders versus non-responders, which is in line with findings from Caposiena Caro *et al.*[24] who reported a significant

association between HiSCR and IHS4 scores. Furthermore, the post hoc analysis showed that while more patients with medium and high AN count at baseline responded to treatment, proportionally a larger decrease in IHS4 scores was measured in these AN count groups than in patients with low AN counts at baseline.

Among HiSCR responders, an important increase in the number of patients with mild HS and the decrease in patients with low and medium AN counts in the severe HS category were observed at weeks 24 and 52. Some improvement in HS severity detected in non-responders at week 52 may be associated with improvement of partial responders, that is those with a 25% reduction in AN count without any increase in the number of abscesses or draining fistulas relative to baseline.

The majority of changes observed in patients assessed as HWS III were in the high AN count group, which is coherent with the findings in responders. Interestingly, Frew *et al.*[17] reported a significant association between Hurley stage III and the IHS4 category change (odds ratio = 0.57; 95% CI: 0.33, 0.95; $P = 0.03$).

Limitations of the research methods used in this study are related to, but may not have been limited to, the observational nature of the study with regard to missing data, which has been alleviated with the use of sensitivity analyses for the primary endpoint. Comparing our data with clinical trial data may lead to bias due to the more stringent inclusion criteria and different patient management in clinical trials. Furthermore, in the post hoc analysis the low number of patients in some of the subgroups may have limited the interpretation of the results.

In a real-world setting, adalimumab effectiveness observed at week 24 in patients with moderate-to-severe HS was maintained at week 52. Future investigations should consider the primary endpoint to be at 24 weeks, as done in clinical trials on psoriasis.[25,26] Patients with medium and high AN counts at baseline tended to respond better than those with a low AN count, which was generally reciprocated with changes in HS severity during the study in responder patients. SOLACE provides an external validity to clinical studies measuring the effectiveness of adalimumab in patients with HS and also to the use of IHS4 as an indicator of clinical response in a real-world setting. The safety data reported during the study were consistent with the known safety profile of adalimumab, and no new safety signal or unexpected trend was identified for the SOLACE population.[3,5,27-29]

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Affected body areas
Figure S2 Abscesses, inflammatory nodules, and draining fistulas in week-24 non-responders
Figure S3 IHS4 scores, HS disease severity, and HWS in 24-week non-responders
Table S1 SOLACE Canadian principal investigators and sites
Table S2 Mean change from baseline in HS lesion count (ITT population)
Table S3 Patients who experienced flare (ITT population)
Table S4 HiSCR at week 24: Potential prognostic factors (ITT population)