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Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa
The SHARPS Randomized Clinical Trial

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IMPORTANCE Surgery is a mainstay in the management of hidradenitis suppurativa (HS). Adalimumab is the first drug approved for HS.

OBJECTIVE To investigate the efficacy and safety of adalimumab in combination with wide-excision surgery followed by secondary intention healing.

DESIGN, SETTING, AND PARTICIPANTS The Safety and Efficacy of Adalimumab for Hidradenitis Suppurativa Peri-Surgically (SHARPS) trial was a phase 4, randomized, double-blind, placebo-controlled study of adalimumab in conjunction with surgery. Patients were enrolled in 45 sites across 20 countries from July 18, 2016, to February 2, 2019, with the last patient visit on October 16, 2019. Eligible patients (aged 18-65 years) had moderate to severe HS that required radical surgery in an axillary or inguinal region and had 2 other anatomical regions affected, with 1 or more regions at Hurley stage II or III. Analysis was conducted in November 2019.

INTERVENTIONS Patients were randomized 1:1 to receive continuous adalimumab, 40 mg, or placebo during presurgery (12 weeks), perioperative (2 weeks), and postoperative (10 weeks) periods.

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients achieving HS clinical response across all body regions at week 12.

RESULTS Overall, 103 patients were randomized to adalimumab and 103 to matching placebo. Among all patients, 51% (n = 106) were women, 94% (n = 193) were White, and the mean (SD) age was 37.6 (11.3) years. At week 12, significantly more patients receiving adalimumab (49 of 103 [48%]) vs placebo (35 of 103 [34%]; P = .049) achieved HS clinical response across all body regions (treatment difference, 14% [95% CI, 0%-27%]). Treatment-emergent adverse events were reported in 74 of 103 patients (72%) and 69 of 103 patients (67%) in the adalimumab and placebo groups, respectively. No increased risk of postoperative wound infection, complication, or hemorrhage was observed with adalimumab vs placebo. Two deaths occurred in the adalimumab group; neither was considered as having a reasonable possibility of relationship to study drug.

CONCLUSIONS AND RELEVANCE Adalimumab was efficacious in conjunction with wide-excision surgery followed by secondary intention healing, with no need to interrupt treatment prior to surgery. These data support further investigation of adalimumab as an adjuvant therapy to surgery in patients with moderate to severe HS.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02808975

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com

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Hidradenitis suppurativa (HS), a chronic recurrent inflammatory skin disease of the hair follicle, manifests with deep-seated, painful nodules, abscesses, sinus tract formation, and subsequent scarring, most commonly localized in the axillary, inguinal, and anogenital regions.[1-3] The tissue destruction and scarring has historically led to the belief that HS is also a surgical disease.[4] Patients are generally treated with surgery owing to extensive sinus tract/fistula/tunnel formation, destruction of anatomic feature and/or function, and eventually contracted painful scars.[3,5] However, postsurgical recurrence may occur in up to 70% of patients, depending on the type of procedure performed and the anatomic surgical site.[1] Wide-excision surgery, the most radical and invasive procedure used for HS, is reported with low recurrence rate for primary and secondary intention healing.[5,6] Although surgical management may be performed for the most severe lesions, patients may have lesions in other anatomical areas and therefore require anti-inflammatory treatment simultaneously with surgical management.[6,7] The European S1 HS guidelines suggest that treatment is based on individual subjective effect and objective severity of disease.[1]

Adalimumab was efficacious and well tolerated in previous HS studies (including the phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects With Moderate to Severe Hidradenitis Suppurativa [PIONEER] I and II trials) and is globally indicated for the treatment of moderate to severe HS.[8-12] However, placebo-controlled data are not available on the effect of adalimumab on HS lesions in patients concomitantly undergoing surgery from previous studies.[9,11,12] Findings from case series and observational studies suggest that when used in combination with radical surgical resection, the immunomodulating effects of biologics may augment the results of surgery.[7,13-15] The objective of the Safety and Efficacy of Adalimumab for Hidradenitis Suppurativa Peri-Surgically (SHARPS) study was to assess the efficacy and safety of adalimumab in conjunction with surgery in adults with moderate to severe HS.

Key Points

Question What is the efficacy and safety of adalimumab in conjunction with surgery in adult patients with moderate to severe hidradenitis suppurativa (HS)?

Findings In this randomized clinical trial of 206 patients, significantly more patients receiving adalimumab achieved HS clinical response across all body regions vs placebo at week 12 and improvements in quality of life.

Meaning Adalimumab was efficacious in patients with HS, with no need to interrupt treatment prior to surgery; these findings may help to guide medical treatment decisions for patients with HS who are candidates for surgery.

Methods

Study Design

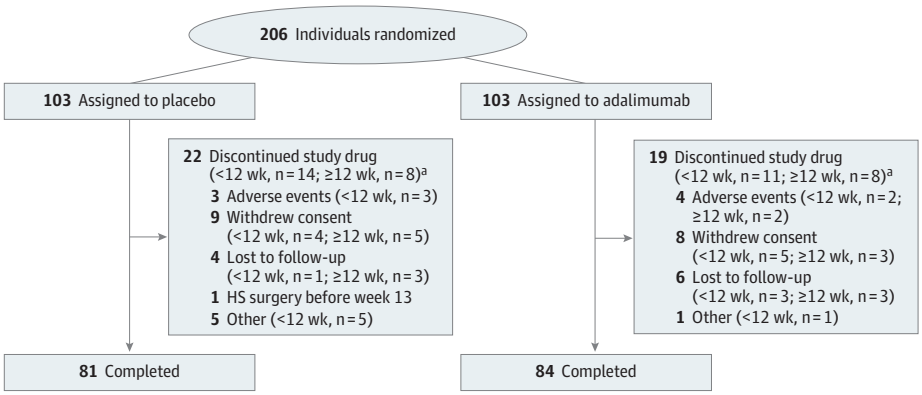
The SHARPS study was a global, phase 4, prospective, multicenter, randomized, double-blind, placebo-controlled study of adalimumab in conjunction with surgery in adults with moderate to severe HS who were surgical candidates. The study protocol (Supplement 1) was approved by an independent ethics committee or institutional review board at each study site (eTable in Supplement 2). Eligible patients (random sample) were enrolled at 45 sites worldwide (eTable in Supplement 2). All patients provided written informed consent. The study consisted of a 30-day screening period, an initial 12-week presurgery double-blind treatment period, a 2-week perioperative double-blind treatment period, and a subsequent 10-week postoperative double-blind treatment period (eFigure 1 in Supplement 2). The study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and the Declaration of Helsinki.[16]

During the presurgery period, patients were randomized 1:1 (eMethods in Supplement 2) to subcutaneous adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg weekly thereafter) or placebo. The designated surgeon recorded the projected size of the surgical excision during the screening period. During the perioperative period (weeks 13 and 14), patients continued adalimumab, 40 mg, weekly or placebo, and the surgeon measured and recorded the surface area of the actual surgery. Wide-excision (complete excision of lesion with more than 50% but leaving parts of the anatomic area) surgery of either 1 axillar or 1 inguinal region that contained at least 1 active HS lesion and required excisional surgery as assessed by the designated surgeon occurred during week 13, followed by secondary intention healing. Surgery and postoperative management (eg, hospitalization, surgical wound care) was per local practice. During the postoperative period, patients continued adalimumab, 40 mg, weekly or placebo (weeks 15-23); no study drug was administered at the final study visit at week 24.

Study Participants

The first patient was enrolled on July 18, 2016, and the last patient completed their last visit on October 16, 2019. SHARPS enrolled adults (aged 18-65 years) diagnosed with HS 1 year or more prior to baseline. Eligible patients had 3 or more regions with inflammatory (active) HS lesions, including an axilla or unilateral inguinal region requiring excisional surgery (that was defined as the HS surgical site), and 1 or more other HS region at Hurley stage II or III. The HS surgical site had to include 1 or more active HS lesions (ie, 1 axilla or 1 inguinal lesion) that required excisional surgery and was large enough to require healing by secondary intention as assessed by a designated surgeon. Nonsurgical sites were required to have a total abscess and inflammatory nodule (AN) count of 3 or more at baseline visit. Patients with a baseline draining fistula count of more than 20; those requiring surgical management before week 13; those requiring excisional surgery with primary closure, partial surgical reduction of excision with surgical suture, or reconstruction techniques; and those with active skin disease or conditions other than HS that could interfere with the

Figure 1. Patient Disposition



HS indicates hidradenitis suppurativa.

[a] Primary reason for discontinuation given.

assessment of HS were excluded. Data on race were self-reported.

Outcomes

The primary efficacy end point was the proportion of patients at week 12 who achieved HS clinical response (HiSCR), defined as a reduction of 50% or more in AN count with no increase in count of abscess and draining fistula relative to baseline across all body regions.

The 4 ranked secondary end points included proportion of patients achieving HiSCR excluding the surgical site at week 12, proportion of patients achieving HiSCR excluding the surgical site at week 24, percentage change in surface area of the HS surgical site from baseline to week 12, and proportion of patients at week 12 who required less extensive surgery than the surgical plan (as determined at baseline) or required no surgery as determined by the designated surgeon.

Other efficacy end points included change from baseline in high-sensitivity C-reactive protein, Dermatology Life Quality Index, HS Patient's Global Assessment of Skin Pain, HS Impact Assessment, and HS Symptom Assessment and the proportion of patients who experienced a flare (defined as a ≥25% increase in AN count with a ≥2 increase relative to baseline) at each study visit.[17,18]

Safety assessments included treatment-emergent adverse events (AEs), physical examinations, laboratory variables, and vital signs. A treatment-emergent AE was defined as any AE with onset or worsening after the first study drug administration and with an onset date no more than 70 days after the last dose of study drug.

Statistical Analyses

The study was designed to enroll approximately 200 patients. Based on the combined response rates for the HiSCR from previous studies,[9] a conservative estimate of 20% treatment difference was used for the power calculation in which case 100 patients per treatment arm would provide at least 80% power to detect a treatment difference at the alpha level of .05 and to demonstrate the point estimate of the treatment difference of at least 15% for the primary end point. The primary efficacy analysis was conducted in the intent-to-treat population, which included all randomized patients. A post hoc sensitivity analysis of primary and ranked secondary end points excluding patients who did not meet the key lesion entry criterion (AN count ≥3 within the HS nonsurgical sites at baseline) was also conducted.

Missing data were imputed using nonresponder imputation for categorical end points and last observation carried forward for continuous end points for the efficacy analyses, except for the 2 surgery-related efficacy end points, which were analyzed using as-observed cases. Lesions that received intervention (eg, those contained within the excised surgical specimen or any protocol-allowed minor interventions including incision and drainage) were counted as permanently present from the date of the study drug intervention.

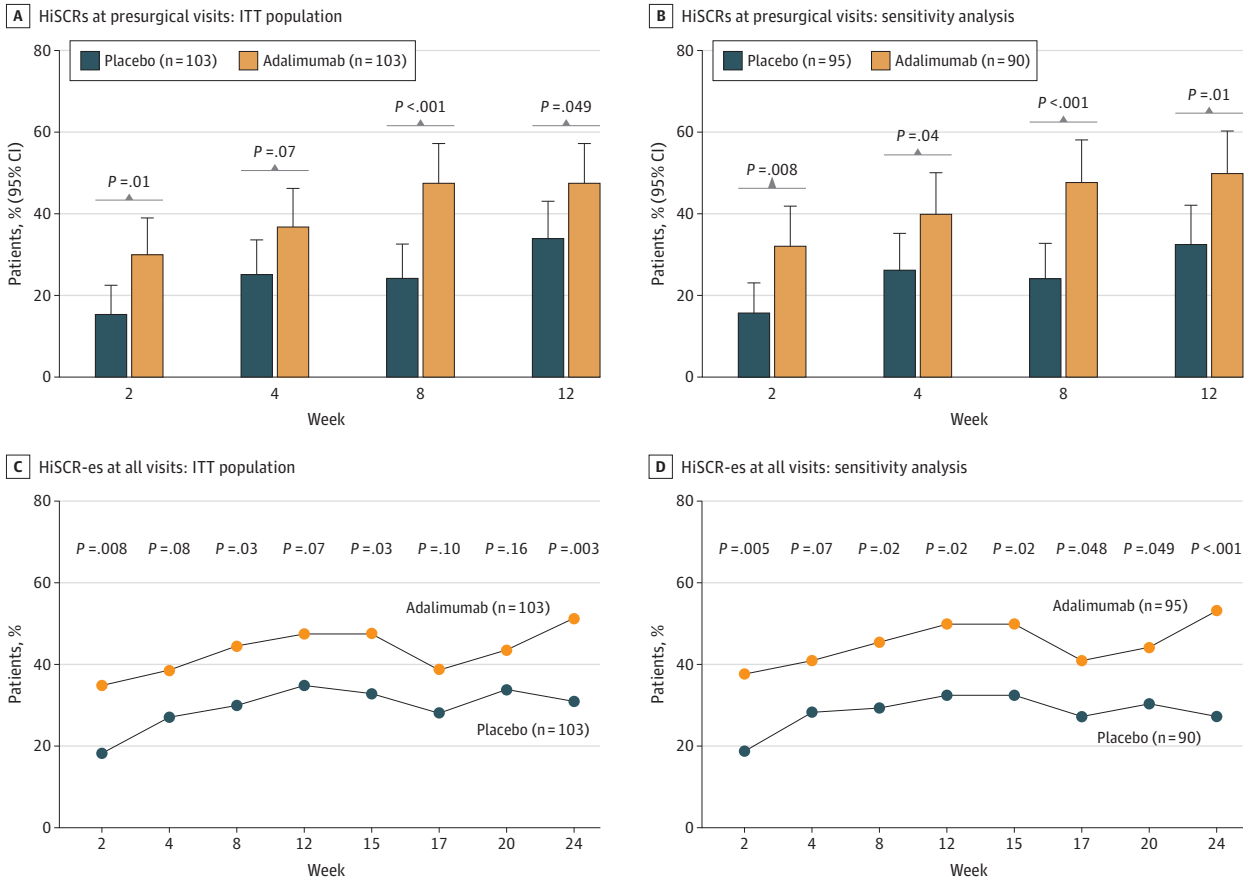
The safety population was defined as all patients in the intent-to-treat population who received 1 or more doses of study drug. For the safety analyses, the patient was analyzed according to the treatment they actually received.

Categorical variables were analyzed using Cochran-Mantel-Haenszel test, stratified by baseline Hurley stage and anatomical location of the HS surgical site and continuous variables using analysis of covariance, with treatment, baseline Hurley stage, anatomical location of the HS surgical site, and baseline values in the model. To control for type I error, statistical comparisons for the primary efficacy end point and ranked secondary end points were carried out in hierarchical order under a 2-sided significance level of .05. Analyses were performed using SAS statistical software version 9.4 (SAS Institute). The numbers and percentages of patients experiencing treatment-emergent AEs were tabulated using the Medical Dictionary for Drug Regulatory Activities, version 22.0, system organ classes and preferred terms. Analysis was conducted in November 2019.

Results

A total of 206 patients were randomized, and 165 patients (80%) completed the 24-week study (**Figure 1**). Most discontinuations occurred prior to week 12 (n = 25); the primary reasons for discontinuation were withdrawal of consent (n = 17)

Figure 2. Patients Achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Presurgical Visits and Achieving HiSCR-es at All Visits



Patients achieving HiSCR at presurgical visits in the intent-to-treat (ITT) population (A) and in sensitivity analysis (B) and patients achieving HiSCR excluding the surgical site (HiSCR-es) at all visits in the ITT population (C) and in sensitivity analysis (D). Post hoc sensitivity analyses were conducted to exclude the 21 patients with baseline abscess and inflammatory nodule of less than 3 at the hidradenitis suppurativa nonsurgical site (ie, did not meet the key lesion entry criterion of baseline abscess and inflammatory nodule count of ≥3 at hidradenitis suppurativa nonsurgical sites). All panels represent nonresponder imputation analyses. The primary end point was HiSCR at week 12. The first ranked secondary end point was HiSCR-es at week 12 and the second ranked secondary end point was HiSCR-es at week 24. A and B, *P* values for visits other than week 12 are nominal *P* values without controlling for overall type I error. C and D, *P* values for visits other than weeks 12 and 24 are nominal *P* values without controlling for overall type I error.

and loss to follow-up (n = 10). Of 206 randomized patients, 21 did not meet the key lesion entry criterion and were excluded from the sensitivity analyses. The mean (SD) duration of exposure was similar between groups (159.2 [40.3] days for adalimumab and 156.2 [40.6] days for placebo), and the mean treatment compliance was 95.3% and 95.9%, respectively. Among all patients, 51% (n = 106) were women, 94% (n = 193) were White, and the mean (SD) age was 37.6 (11.3) years (**Table 1**).

The proportion of patients achieving HiSCR across all body regions was significantly higher in patients receiving adalimumab vs placebo at week 12 (*P* = .049; treatment difference, 14% [95% CI, 0%-27%]) (**Figure 2**A). Similar results were observed in the sensitivity analysis at week 12 (*P* = .02; treatment difference, 18% [95% CI, 3%-32%]) (Figure 2B).

For the ranked secondary end points, the proportion of patients who achieved HiSCR excluding the surgical site was numerically but not significantly higher in patients receiving adalimumab vs placebo (*P* = .07; treatment difference, 13% [95% CI, -1% to 26%]) at week 12; however, significant differences were observed at week 24 (*P* = .003; treatment difference, 20% [95% CI, 7%-34%]) (Figure 2C). In the sensitivity analysis, a significantly greater proportion of patients receiving adalimumab vs placebo achieved HiSCR excluding the surgical site at week 12 (*P* = .02; treatment difference, 18% [95% CI, 3%-32%]) and at week 24 (*P* < .001; treatment difference, 26% [95% CI, 12%-40%]) (Figure 2D).

Outcomes were comparable between groups for the remaining ranked secondary end points: mean percentage changes from baseline in the surface area of the HS surgical site (*P* = .31; least squares treatment difference, 42.0 [95% CI, -40.0 to 123.9]) and the proportions of patients who required less extensive surgery than the surgical plan or no surgery at week 12 (*P* = .75; treatment difference, 3% [95% CI, -13% to 18%]) (**Figure 3**). The sensitivity analyses supported the lack of differences for these 2 secondary end points (Figure 3).

Additional efficacy end points (change from baseline in high-sensitivity C-reactive protein, Dermatology Life Quality Index, HS Patient's Global Assessment of Skin Pain, HS Im-

Table 1. Patient Demographic and Disease Characteristics

Characteristic	No. (%)		
	Placebo	Adalimumab	Overall
Total No.	103	103	206
Women	55 (53)	51 (50)	106 (51)
Men	48 (47)	52 (50)	100 (49)
Age, mean (SD) [range], y	36.8 (10.8) [18-63]	38.5 (11.7) [18-64]	37.6 (11.3) [18-64]
Race[a]			
White	97 (95)[b]	96 (93)	193 (94)[b]
Black or African American	4 (4)[b]	4 (4)	8 (4)[b]
BMI	31.7 (7.1)[c]	32.6 (7.1)	32.1 (7.1)[c]
Current use			
Tobacco	70 (69)[b]	69 (68)[b]	139 (68)[c]
Alcohol	52 (53)[d]	51 (52)[e]	103 (52%)[f]
HS			
Family history	21 (20)	28 (27)	49 (24)
Duration, mean (SD), y	10.0 (9.0)	11.7 (10.5)	10.9 (9.8)
Prior surgery	67 (65)	63 (61)	130 (63)
Hurley stage			
II	54 (52)	53 (51)	107 (52)
III	49 (48)	50 (49)	99 (48)
Planned surgery site			
Axilla	61 (59)	60 (58)	121 (59)
Inguinal region	42 (41)	43 (42)	85 (41)
Planned surgical area, mean (SD), cm^2	34.4 (34.8)	33.8 (34.5)	34.1 (34.6)
Median	23.4	24.0	24.0
No.	102	102	204
Hurley stage II			
Axilla surface area, cm^2			
Mean (SD)	26.7 (28.1)	27.6 (20.5)	27.1 (24.5)
Median	17.0	25.0	20.0
No.	31	30	61
Inguinal region surface area, cm^2			
Mean (SD)	28.1 (31.6)	44.0 (46.2)	36.2 (40.1)
Median	18.5	33.0	24.0
No.	22	23	45
Hurley stage III			
Axilla surface area, cm^2			
Mean (SD)	49.6 (42.4)	35.0 (36.9)	42.3 (40.1)
Median	41.0	24.0	26.3
No.	30	30	60
Inguinal region surface area, cm^2			
Mean (SD)	30.3 (29.5)	29.3 (31.3)	29.8 (30.0)
Median	22.5	18.0	19.0
No.	19	19	38
AN count, mean (SD)	11.3 (12.6)	10.3 (7.5)	10.8 (10.3)
Abscess count, mean (SD)	2.8 (6.1)	2.4 (3.7)	2.6 (5.1)
Inflammatory nodule count, mean (SD)	8.5 (9.1)	7.9 (5.5)	8.2 (7.5)
Draining fistula count, mean (SD)	4.0 (5.4)	3.6 (4.0)	3.8 (4.7)
hs-CRP, mean (SD), mg/dL	1.58 (1.95)[b]	1.17 (1.88)[b]	1.38 (1.92)[c]
HS-PGA-SP, worst skin pain, mean (SD)	4.8 (2.9)	5.0 (2.9)[b]	4.9 (2.9)[b]
Total score, mean (SD)			
DLQI	12.9 (7.1)[c]	13.6 (7.3)[b]	13.2 (7.2)[g]
HSSA	5.9 (2.5)[b]	6.0 (2.4)[b]	5.9 (2.5)[c]
HSIA	5.1 (2.3)[b]	4.8 (2.5)	4.9 (2.4)[b]

Abbreviations: AN, abscess and inflammatory nodule; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DLQI, Dermatology Life Quality Index; HS, hidradenitis suppurativa; hs-CRP, high-sensitivity C-reactive protein; HSIA, HS Impact Assessment; HS-PGA-SP, HS Patient's Global Assessment of Skin Pain; HSSA, HS Symptom Assessment.

SI conversion factor: To convert hs-CRP to milligrams per liter, multiply by 10.

[a] Other race included Asian, American Indian or Alaskan Native, and missing.

[b] Data missing for 1 patient.

[c] Data missing for 2 patients.

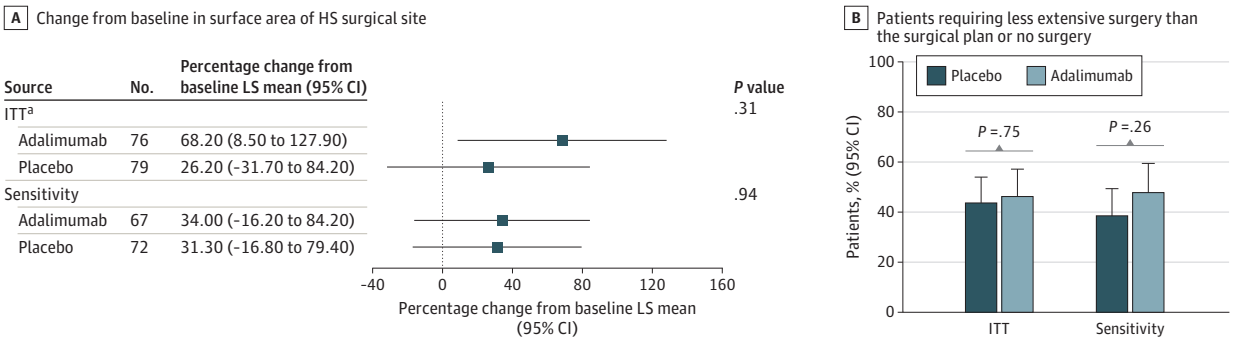
[d] Data missing for 5 patients.

[e] Data missing for 4 patients.

[f] Data missing for 9 patients.

[g] Data missing for 3 patients.

Figure 3. Change From Baseline in Ranked Secondary Surgical End Points at Week 12



Change from baseline in surface area of hidradenitis suppurativa (HS) surgical site (A) and patients requiring less extensive surgery than the surgical plan or no surgery (B). Intent-to-treat (ITT) and post hoc sensitivity analyses are presented for both panels. Post hoc sensitivity analyses were conducted to exclude the 21 patients with baseline abscess and inflammatory nodules less than 3 at the HS nonsurgical site (ie, did not meet the key lesion entry criterion of baseline abscess and inflammatory nodule count of ≥3 at the HS nonsurgical site). Both panels represent an as-observed analysis approach. LS indicates least squares.

[a] A positive percentage change indicates an increase in the actual surgical area at week 13 compared with the planned surgical area at baseline, with few extreme observations (n = 3) of an increase more than 1000%.

pact Assessment, HS Symptom Assessment, and proportion of patients who experienced a flare) also showed improvements with adalimumab vs placebo (eFigures 2-6 in Supplement 2). Fewer patients treated with adalimumab experienced a flare during the 12-week presurgery period (across all body regions) and during the entire 24-week study (across nonsurgical sites) vs placebo (eFigure 3A in Supplement 2), which was supported by the sensitivity analyses (eFigure 3B in Supplement 2). Clinically meaningful improvements (defined as a change from baseline of 1 to 2 points) in HS Impact Assessment overall score (at weeks 4, 12, and 24) and in HS Symptom Assessment overall score (at weeks 4, 12, and 15) were observed with adalimumab vs placebo (eFigure 6 in Supplement 2).

Treatment-emergent AEs and serious AEs were comparable between treatment groups (**Table 2**). Four patients discontinued study drug owing to AEs in both groups; in the adalimumab group, 3 discontinued owing to serious AEs. No other cases of opportunistic infections, tuberculosis, lymphoma, nonmelanoma skin cancer, or demyelinating disorder were reported in the adalimumab group during the study. Two deaths occurred in the adalimumab group (neither was considered study drug related) (Table 2).

The most common AEs were nasopharyngitis, worsening of hidradenitis, procedural pain, headache, arthralgia, and diarrhea (Table 2). The frequency of these AEs was similar in both groups, with the exception of procedural pain and arthralgia that were reported more frequently with adalimumab and assessed by the investigator to have no reasonable possibility of being study drug related in most patients (procedural pain: 14 of 14 patients; arthralgia: 4 of 6 patients). No increased risk of postoperative wound infection, complication, or hemorrhage was observed with adalimumab vs placebo (Table 2). Two occurrences of wound complication were reported in 1 patient receiving placebo; both were categorized as irritations of the skin (ie, eczematous changes) surrounding the surgical wound and were thought to be due to the fixation material of the wound dressing.

Discussion

The SHARPS study is the first randomized placebo-controlled trial of a tumor necrosis factor inhibitor used in conjunction with surgery, to our knowledge. The results of this study demonstrate that adalimumab is an effective and safe adjunctive therapy to surgery when continued during the perioperative and postoperative periods, improving systemic inflammation in patients undergoing wide-excision surgery followed by secondary intention healing. Importantly, no increased risk of postoperative wound infection or complication was reported with adalimumab. Furthermore, 12-week adalimumab treatment was efficacious at decreasing the inflammatory load and reducing the number of HS inflammatory lesions across all body regions presurgery and clinically meaningful decreases in patients' worst skin pain due to HS, reductions in overall HS symptoms and effect, and improvements in quality of life were observed throughout the study with adalimumab. Taken together, these results may guide medical decision-making for surgeons/dermatosurgeons and dermatologists on the best approach to treat moderate to severe HS in patients who are candidates for surgery.

Combined medical and surgical therapy is endorsed in all current guidelines in the management of moderate to severe HS,[1,19,20] and previous studies have demonstrated that this can be a successful strategy. In a retrospective analysis of 21 patients, lower recurrence (4 of 29 sites vs 10 of 26 sites; $P < .01$) and disease progression (18% vs 50% of patients; $P < .001$) was observed among patients receiving postoperative (14-20 days) adjuvant biologic therapy for at least 6 months vs patients treated with surgery alone.[14] Similarly, in a prospective, survey-based study of 39 patients, no relapse after surgery was reported in patients receiving preoperative or postoperative (within 2 months) tumor necrosis factor therapy compared with a 23.7% overall relapse rate for all patients.[15] The SHARPS study further supports the use of biologic therapy in conjunction with surgery in the population with moderate to severe HS who may have a sub-

Table 2. Summary of Treatment-Emergent Adverse Events

Adverse event	No. (%)	
	Placebo	Adalimumab
Total No.	103	103
Adverse event		
Any	69 (67)	74 (72)
Possibly related to study drug	26 (25)	36 (35)
Severe	6 (6)	9 (9)
Serious	3 (3)[a]	7 (7)[b]
Possibly related to study drug	0	1 (1)
Leading to discontinuation of study drug	4 (4)[c]	4 (4)[d]
Infection	38 (37)	41 (40)
Serious infection	1 (1)	2 (2)
Malignant neoplasm	0	1 (1)[e]
Postoperative wound		
Complication	1 (1)	0
Infection	1 (1)	1 (1)
Postprocedural hemorrhage	1 (1)	1 (1)
Adverse event leading to death	0	1 (1)
All deaths occurring after last dose, d	0	2 (2)[f]
≤70	0	1 (1)
>70	0	1 (1)
Adverse events occurring in >5% of patients in either treatment population		
Nasopharyngitis	19 (18)	19 (18)
Hidradenitis worsening	15 (15)	14 (14)
Procedural pain	8 (8)	14 (14)
Headache	14 (14)	13 (13)
Arthralgia	1 (1)	6 (6)
Diarrhea	4 (4)	6 (6)
Dizziness	6 (6)	2 (2)

[a] Serious adverse events in patients receiving placebo included cardiovascular disorder and worsening of hidradenitis, postoperative wound infection, and worsening of hidradenitis.

[b] Serious adverse events in patients receiving adalimumab included cholelithiasis, blastocystis infection, respiratory tract infection, musculoskeletal chest pain, testicular cancer, ruptured cerebral aneurysm, and pain in extremity.

[c] Adverse events leading to discontinuation of study drug in patients receiving placebo included chest pain, blood creatine phosphokinase level increase, myopathy, and dizziness in 1 patient and worsening of hidradenitis in 3 patients.

[d] Adverse events leading to discontinuation of study drug in patients receiving adalimumab included blastocystis infection, testicular cancer, ruptured cerebral aneurysm, and headache; 3 of these were serious (in 2 patients, the adverse events were assessed as having no reasonable possibility of relationship to study drug, and the third discontinued because of a serious adverse event of *blastocystis hominis* infection assessed by the investigator as having a reasonable possibility of being study drug related).

[e] Testicular cancer.

[f] Death resulting from treatment-emergent adverse event of ruptured cerebral aneurysm (patient died 4 days after receiving the last dose of adalimumab) and posttreatment death [day 503] from natural causes secondary to hypertrophic cardiomyopathy).

stantial disease burden and require major HS surgery.[9] Specifically, the SHARPS population was comparable with the population in the pivotal PIONEER studies, with the exception that more patients reported prior HS surgery (63% [SHARPS study] vs 12% [PIONEER studies]) and a status of candidate for surgery was required for enrolment in the SHARPS study but was an exclusionary criterion in the PIONEER studies.[9,21]

A significantly greater percentage of patients receiving adalimumab achieved HiSCR across all body regions at week 12 vs placebo (difference vs placebo, 14%), confirming adalimumab efficacy from earlier studies.[9-11,22] The magnitude of improvement in HiSCR observed with adalimumab was greater in the PIONEER studies (difference vs placebo, 24%)[17] than observed here; however, the SHARPS patient population required a combination of medical and surgical treatments and thus likely represents a population with more advanced disease.[9-11,22,23] Furthermore, SHARPS demographics described a slightly less inflammatory population (based on lower inflammatory nodule count although similar number of draining fistula) than seen in earlier studies, suggesting that the inflammatory target for adalimumab may have been smaller in the SHARPS population, rendering adalimumab less efficacious.[9-11,21,22] Lower inflammatory nodule counts at baseline may also increase the volatility of the HiSCR because smaller absolute changes are more likely to influence the calculation. Among patients receiving placebo in the SHARPS study, HiSCR was numerically higher vs the PIONEER studies (34% vs 27%)[9,21] and may reflect greater levels of patient involvement in SHARPS because of the required presurgical examinations and complex surgical plans. Alternatively, the observed differences in HiSCR in the placebo groups could also be due to disease variations among the populations enrolled in each study.[9,21]

At week 12 (presurgery period) and at week 24 (postoperative period), the proportion of patients who achieved HiSCR excluding the surgical site was numerically higher with adalimumab vs placebo, with significant differences demonstrated in the sensitivity analysis. These findings demonstrate that adalimumab is generally effective at reducing HS inflammatory lesions across body regions through 24 weeks of treatment even in the setting of wide-excision surgery midway through the treatment period. However, a drop in HiSCR excluding the surgical site was observed at week 17. This may be due to a general immune suppression response following major surgery,[24] inflammation resulting from the liberation of antigens from the surgical site or wound healing,[25] particularly in wound healing by secondary intention, or the result of stress caused by surgery in one area leading to flares in other body areas.[26]

The ranked secondary surgical end points (mean change in surface area of HS surgical site and proportion of patients requiring less extensive surgery than the surgical plan or no surgery) were comparable between treatment groups. The lack of response to adalimumab in these secondary surgical end points may result from the study being powered to achieve the primary end point only. Furthermore, both of these surgical end points were strictly exploratory in nature and meant to guide future study design. Excisional surgery is generally targeted to more severe Hurley stage III lesions or chronic lesions with no signs of inflammation for a prolonged period[19] and thus may be less affected by an anti-inflammatory treatment such as adalimumab.

No new safety findings were reported during the SHARPS study, confirming the safety profile of adalimumab from previous HS studies.[9-11,22,27] Importantly, no increased risk of post-

operative wound infection or complication was observed with adalimumab. However, procedural pain was observed in 14% (14 of 103) and 8% (8 of 103) of patients treated with adalimumab and placebo, respectively, and included all AEs that were reported with event descriptions of postoperative pain, pain after surgery at the surgical site, or similar. All of these patients received pain medications, which were specifically used for postsurgical pain following wide excision of the skin. These AEs were assessed by the investigator to have no reasonable possibility of relationship to study drug in all patients except for 1 patient receiving placebo. Therefore, no direct treatment association may be drawn from these observations.

In this study, secondary healing was chosen because it is the most frequently applied technique and carries less risk of recurrence. In addition, the anatomic areas were limited resulting in less necessity for reconstructive techniques (eg, just excision of the groin but not adjacent anatomic areas, which would have made a reconstruction necessary).

Limitations

This study is not without limitations. Only wide-excision surgery followed by secondary intention healing was assessed in this study and not other options of closure or secondary reconstruction. Although this is the first randomized placebo-controlled study of adalimumab in conjunction with surgery in patients with HS, to our knowledge, further studies are needed to confirm these results, especially the role of adalimumab in postsurgical wound healing. Across several outcomes, the observed efficacy with adalimumab improved after post hoc sensitivity analyses were applied to exclude 21 patients who did not have AN count of 3 or more across HS nonsurgical sites at baseline.

Conclusions

In conclusion, adalimumab treatment was efficacious in conjunction with wide-excision surgery (followed by secondary intention healing) for moderate to severe HS, indicating no need to interrupt adalimumab treatment prior to surgery. The safety profile was consistent with previous studies of adalimumab in HS. Overall, these results support further investigation of adalimumab as an adjunctive therapy to surgery in patients with moderate to severe HS.

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