Clinical response rates, placebo response rates, and significantly associated covariates are dependent on choice of outcome measure in hidradenitis suppurativa: A post hoc analysis of PIONEER 1 and 2 individual patient data

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Background: The hidradenitis suppurativa clinical response (HiSCR) is the gold standard primary outcome measure for hidradenitis suppurativa clinical trials; however, it does not assess the presence of draining tunnels, a common finding in advanced disease. It is unclear what the effect of the presence or absence of draining tunnels has on the efficacy of adalimumab therapy in moderate and advanced disease.

Objectives: We evaluated the efficacy of adalimumab versus placebo using the International Hidradenitis Suppurativa Severity Scoring System (IHS4). Additionally, we assessed the effect of draining tunnels on therapeutic response as measured by both the HiSCR and change in nodule counts.

Methods: Reanalysis was conducted with the IHS4 and PIONEER 1 and 2 individual patient data. Both binary outcomes (achieving HiSCR and achieving change in IHS4 severity category) and continuous outcomes (nodule counts and IHS4 score) were calculated with R. Regression modeling was undertaken to assess the effect of draining tunnels and other variables. $P < .05$ was considered statistically significant.

Results: The significance of adalimumab therapy depended on the outcome measure used. Placebo response rates were highest when binary outcome measures were used. Draining tunnels, smoking, antibiotics, and body mass index influenced HiSCR response in PIONEER 2. Significant differences in disease severity were observed between PIONEER 1 and 2 data sets.

Conclusions: Elevated placebo response rates in PIONEER 1 and 2 are partially attributable to the use of binary outcome measures. Draining tunnels influence clinical response as measured by HiSCR and nodule

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BACKGROUND

The hidradenitis suppurativa clinical response (HiSCR)[1] outcome measure is currently considered the gold standard primary outcome measure for the assessment of new pharmacologic interventions in hidradenitis suppurativa clinical trials.[1,2] HiSCR is defined as a 50% reduction in abscess and nodule count without any increase in the number of abscesses or draining tunnels relative to baseline.[1] However, high rates of placebo response have been identified and are problematic for the evaluation of novel pharmacologic interventions in this disease.[3] As such, studies using the HiSCR may be prone to measurement bias when comparing different stages and severities of disease.[4] The International Hidradenitis Suppurativa Severity Scoring System[5] (IHS4), developed by the European Hidradenitis Suppurativa Foundation Investigator Group, is an alternative outcome measure that is often included as a secondary outcome, but to our knowledge the results of this outcome measure have not been reported in any phase 3 clinical trial to date, nor have there been any attempts to compare different outcome measures using the same clinical trial data set. This comparison would enable the identification of specific clinical variables that may predict response to therapy and also allow the evaluation of measurement bias within specific outcome measures themselves.

Given the heterogeneous clinical manifestations of hidradenitis suppurativa[6] (including nodules, abscesses, tunnels, and scarring), the quantification of abscesses and nodules as an outcome measure (HiSCR) does not take into account the response of draining tunnels to pharmacologic therapy.

Given the overall response rates of hidradenitis suppurativa to adalimumab (41.8% and 58.9% in the PIONEER 1 and 2 studies, respectively)[7,8] and the significant dropout rates in existing studies because of lack of efficacy (27%-50%),[7,8] it is important that we understand the effect of draining tunnels on treatment efficacy.

We hypothesized that the presence of draining tunnels in hidradenitis suppurativa has no effect on rates of clinical response to adalimumab therapy. This was assessed through comparison of 2 outcome measures (HiSCR and IHS4, both as binary and continuous variables) within the PIONEER 1 and PIONEER 2 phase 3 clinical trial data set at week 12 compared with baseline (week 0).

Our specific aims included evaluating the efficacy of adalimumab versus placebo using the IHS4 outcome measure in place of HiSCR and assessing the effect of the presence of draining tunnels on clinical response as measured by the HiSCR and change in nodule counts.

CAPSULE SUMMARY

- The hidradenitis suppurativa clinical response clinical end point is the gold standard outcome measure in hidradenitis suppurativa clinical trials. The effect of draining tunnels (in advanced disease) on the measured efficacy of adalimumab in hidradenitis suppurativa is not well described. Other outcome measures (such as the International Hidradenitis Suppurativa Severity Scoring System) include draining tunnels, but no direct comparison of outcome measures within a common data set has been undertaken.
- Clinical response to adalimumab is significantly greater than placebo regardless of the use of outcome measure in PIONEER 2 but not PIONEER 1. Placebo response rates in the PIONEER 1 and 2 phase 3 trials are significantly lower when the hidradenitis suppurativa clinical response is replaced by the International Hidradenitis Suppurativa Severity Score System. Draining tunnels, smoking, antibiotic use, and body mass index are significantly associated with reduced hidradenitis suppurativa clinical response in PIONEER 2, and differences between results of PIONEER 1 and 2 studies are attributable to different disease severities of patient populations.

METHODS

Deidentified individual patient data from PIONEER 1 and 2 studies were made available by AbbVie Inc and accessed through the secure Vivli online platform.[7] Raw data were extracted and compared with the available published data to ensure accuracy.[7] Only data for period A (week 0 to week 12) comparing adalimumab 40 mg weekly versus placebo were included in the analysis to

Abbreviations used:

BMI: body mass index
CI: confidence interval
HiSCR: hidradenitis suppurativa clinical response
IHS4: International Hidradenitis Suppurativa Severity Scoring System
OR: odds ratio

reflect current dosing recommendations. Individuals with incomplete data and those who received antibiotic therapy in PIONEER 1 were excluded from analysis. Antibiotic therapy in PIONEER 2 was included as a covariate. Our statistical methods mirrored those of the PIONEER 1 and 2 statistical analysis,[7] with the exception that the HiSCR (sliding dichotomous variable) was replaced with the IHS4. The IHS4 was expressed as a continuous variable, using available raw individual patient data according to the published equation by Zouboulis et al[5] (nodule count) + (abscess count × 2) + (draining tunnel count × 4). It was also calculated as a sliding dichotomous variable determined by progression to a lower-severity category. Severity categories (mild 0-3; moderate 4-10; severe ≥11) were derived from Zouboulis et al.[5] All data analysis was conducted in R (version 3.5.3; R Core Team, Vienna, Austria).[9]

Each variable of interest was assessed for normality with the Shapiro-Wilk test and histograms. The differences between treatment groups were compared with Welch's *t* test for normally distributed continuous variables and the Mann-Whitney U test for nonnormally distributed continuous variables. Chi-square and Fisher's exact tests were used for categorical variables. Potential associations with the presence of draining tunnels, as well as other a priori potential associations (age, sex, Hurley stage, smoking status, family history, antibiotic use [for PIONEER 2 only], and body mass index [BMI]), were assessed with logistic regression for HiSCR and binary IHS4 and with linear regression for percentage change in IHS4 and absolute change in nodule count. Draining tunnels was not investigated as a covariate in linear or logistic expression when IHS4 was the outcome of interest (because draining tunnels were a component of the IHS4). $P < .05$ was considered statistically significant.

RESULTS

Demographic characteristics of the participants included in the statistical analysis are presented in Table I. The number, percentage, and intergroup differences between adalimumab and placebo arms, as measured by the HiSCR, change in IHS4 severity category, change in nodule counts, and percentage change in IHS4 score are presented in Table II. Statistically significant differences between adalimumab and placebo therapy were observed regardless of whether HiSCR, change in nodule counts, or change in IHS4 score was used as the primary outcome measure (Table II). Change in IHS4 severity category as an outcome measure identified statistically significant change only in PIONEER 2 (Table II). Rates of placebo response were markedly lower when continuous variables (as opposed to sliding dichotomous ones) were used as primary outcome measures (Table II).

Unadjusted logistic regression identified greater odds of HiSCR with adalimumab compared with placebo in PIONEER 1 (odds ratio [OR] 1.98; 95% confidence interval [CI] 1.22-3.26; $P = .006$). When adjusted for covariates, adalimumab therapy displayed greater odds than placebo of association with achieving HiSCR (OR 2.05; 95% CI 1.25-3.47; $P = .005$). No covariates were statistically significant in altering the odds of achieving HiSCR (Table III). Adalimumab had increased odds of association with an HiSCR response in unadjusted analysis of PIONEER 2 (OR 3.77; 95% CI 2.32-6.19; $P < .001$). When covariates were adjusted, patients receiving adalimumab had a further increase in the odds of achieving HiSCR than placebo (OR 4.22; 95% CI 2.50-7.28; $P < .001$). Current smokers had reduced odds of achieving HiSCR compared with nonsmokers (OR 0.56; 95% CI 0.31-0.98; $P = .04$), and the presence of draining tunnels reduced the odds of achieving HiSCR (OR 0.45; 95% CI 0.25-0.79; $P = .01$). In addition, the use of antibiotics reduced the odds of achieving HiSCR (OR 0.47; 95% CI 0.23-0.93; $P = .03$) and every unit increase in BMI significantly reduced the odds of achieving HiSCR by 7.1%. (OR 0.93; 95% CI 0.89-0.97; $P < .001$).

No significant difference in OR was identified between adalimumab and placebo in achieving IHS4 category change in PIONEER 1 (OR 1.58; 95% CI 0.96-2.62; $P = .07$). After adjusting for covariates, adalimumab still did not significantly increase the odds of achieving IHS4 category change versus placebo (OR 1.69; 95% CI 1.00-2.86; $P = .05$). Hurley stage 3 disease significantly reduced the odds of achieving IHS4 category change (OR 0.52; 95% CI 0.30-0.88; $P = .02$). Patients receiving adalimumab had increased odds of achieving IHS4 category change compared with those receiving placebo in PIONEER 2 (OR 2.70; 95% CI 1.66-4.43; $P = <.001$). Adjusting for covariates increased the overall odds (OR 2.91; 95% CI 1.75-4.91; $P = <.001$), with Hurley stage 3 disease (OR 0.57; 95% CI 0.33-0.95; $P = .03$), increase in BMI (OR 0.95; 95% CI 0.91-0.98; $P = .01$), and male sex (OR 0.55; 95% CI

Table I. Population characteristics

	PIONEER 1			PIONEER 2		
Characteristic	**Adalimumab**	**Placebo**	***P* value**	**Adalimumab**	**Placebo**	***P* value**
N	144	145		149	140	
Women	85 (59.0)	100 (69.0)	.10	97 (65.1)	98 (70.0)	.45
Men	59 (41.0)	45 (31.0)		52 (34.9)	42 (30.0)	
White	111 (77.1)	113 (77.9)	.35	130 (87.2)	110 (78.6)	.07
Black	30 (20.8)	25 (17.2)		8 (5.4)	18 (12.9)	
Other	3 (2.1)	7 (4.8)		11 (7.4)	12 (8.6)	
Age, y						
Median	35.0 (28.0, 45.0)	37.0 (30.0, 47.0)	.14	35.0 (27.0, 42.0)	35.0 (26.0, 43.3)	.49
Mean	36.5 ± 11.0	38.4 ± 11.4		34.8 ± 10.1	36.4 ± 12.2	
BMI						
Median	32.1 (27.1, 38.0)	33.9 (28.5, 39.4)	.07	30.3 (26.3, 36.0)	31.3 (26.8, 36.0)	.22
Mean	32.9 ± 7.7	34.6 ± 8.1		30.9 ± 6.4	31.8 ± 6.8	
Hurley stage						
2	80 (55.6)	79 (54.5)	.95	76 (51.0)	79 (56.4)	.42
3	64 (44.4)	66 (45.5)		73 (49.0)	61 (43.6)	
Nicotine use	77 (53.5)	88 (60.7)	.26	96 (64.4)	99 (70.7)	.31
Family history	37 (25.7)	28 (19.3)	.25	36 (24.2)	39 (27.9)	.56
Presence of draining tunnels	108 (75.0)	108 (74.5)	>.99	99 (66.4)	87 (62.1)	.52
Antibiotics	—	—		27 (18.1)	28 (20.0)	.80
Nodules						
Median	8 (4.75, 14)	7 (4, 15)	.88	6 (4,11)	6 (4, 10.25)	.98
Mean	11.4 ± 11.1	11.6 ± 14.2		8.2 ± 6.0	8.8 ± 8.0	
Abscesses						
Median	1.5 (0, 4)	2 (0, 3)	.77	1 (0, 3)	1 (0, 3)	.88
Mean	2.7 ± 3.3	2.6 ± 3.6		2.0 ± 2.5	2.3 (3.2)	
Draining tunnels						
Median	2.5 (0.75, 7)	2 (0, 5)	.38	2 (0, 4)	1 (0, 4)	.60
Mean	4.5 ± 5.1	3.7 ± 4.3		3.0 ± 4.0	3.5 ± 5.8	
Baseline IHS4						
Median	26.5 (15, 45.25)	25.0 (12, 40)	.28	19 (10, 34)	18 (8.75, 32.25)	.91
Mean	34.7 ± 26.8	31.6 ± 27.9		24.2 ± 20.0	27.3 ± 29.3	

Data are reported as no. (%) with median (25th and 75th percentile) and mean ± standard deviation for age, BMI, nodules, abscesses, draining tunnel counts, and baseline IHS4. *P* values were calculated with the χ^2 or Fisher's exact test for categorical variables, Mann-Whitney U test for non-normally distributed continuous data, and Welch's *t* test for normally distributed continuous data. *BMI*, Body mass index; *IHS4*, International Hidradenitis Suppurativa Severity Score; —, not applicable.

0.31-0.96; $P = .04$) significantly reducing the odds of IHS4 category change.

Linear regression identified adalimumab therapy as associated with a mean alteration in nodule count of 2 at week 12 compared with placebo (b = −2.38; 95% CI −4.38 to −0.38; $P = .02$) in PIONEER 1. Accounting for covariates, the association with adalimumab remained significant, implying that, all other covariables being the same, the mean change in nodule count was on average higher by 2 nodules for patients with Hurley stage 3 at week 12 compared with stage 2 (b = 2.23; 95% CI 0.01-4.48; $P = .05$). PIONEER 2 demonstrated a degree of alteration in mean nodule count similar to that of adalimumab therapy in unadjusted analysis (b = −2.54; 95% CI −3.92 to −1.16; $P < .001$) and adjusted analysis (b = −2.58; 95% CI −3.97 to −1.19; $P < .001$). The mean change in nodule count was on average higher at week 12 in the presence of draining tunnels (b = 1.87; 95% CI 0.32-3.43; $P = .02$) compared with the absence of them.

Linear regression identified that adalimumab therapy was associated with an average reduction of 18.74% in IHS4 compared with placebo in unadjusted analysis of PIONEER 1 (b = −18.74; 95% CI −32.97 to −4.57; $P = .01$). With inclusion of covariates, adalimumab treatment was significantly associated with an 18.60% reduction in IHS4 compared with placebo (b = −18.60; 95% CI −33.64 to −3.55; $P = .02$) (Table IV). Unadjusted analysis of PIONEER 2 illustrated a 41.11% reduction in IHS4 with adalimumab compared with placebo (b = −41.11; 95% CI −56.23 to −25.99; $P < .001$). In PIONEER 2, adalimumab therapy was associated

Table II. Comparing hidradenitis suppurativa clinical response and International Hidradenitis Suppurativa Severity Score (as both binary and continuous variables) as primary outcome measures in PIONEER 1 and 2 phase 3 randomized controlled trial data

	PIONEER 1			PIONEER 2		
Outcome measure at week 12	**Adalimumab**	**Placebo**	***P* value**	**Adalimumab**	**Placebo**	***P* value**
N	144	145		149	140	
No. of patients achieving HiSCR (%)	62 (43.06)	40 (27.59)	**.01**	92 (61.74)	42 (30.00)	**<.001**
No. of patients achieving change in IHS4 category (%)	53 (36.81)	39 (26.90)	.09	76 (51.01)	39 (27.86)	**<.001**
Mean change in AN counts (mean % change from baseline)	−5.47 (−33.80)	−2.81 (−13.51)	**.006**	−5.64 (−50.02)	−2.24 (−16.01)	**<.001**
Mean change in IHS4 value (mean % change from baseline)	−11.08 (−30.82)	−4.91 (−12.08)	**.002**	−10.36 (−46.29)	−1.33 (−5.18)	**<.001**

AN, total abscess and inflammatory nodule count; *HiSCR*, Hidradenitis suppurativa clinical response; *IHS4*, International Hidradenitis Suppurativa Severity Score; —, not applicable.
Bold data indicates statistical significance.

Table III. Results of logistic regression models of hidradenitis suppurativa clinical response achievement (model 1) and International Hidradenitis Suppurativa Severity Score category change (model 2) in patients treated with adalimumab and placebo in PIONEER 1 and 2

	PIONEER 1			PIONEER 2		
Variable	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Model 1	Achieving HiSCR					
Adalimumab	**2.08**	**1.25−3.47**	**.005**	**4.23**	**2.51−7.31**	**<.001**
Hurley stage 3	0.91	0.52−1.59	.74	0.64	0.37−1.11	.11
Family history	0.77	0.41−1.40	.40	0.73	0.39−1.32	.30
Current smoker	0.98	0.59−1.65	.94	**0.56**	**0.32−1.0**	**.05**
Presence of draining tunnels	0.63	0.34−1.18	.15	**0.47**	**0.26−0.84**	**.01**
Antibiotic use	—	—	—	**0.48**	**0.24−0.95**	**.04**
BMI	1.01	0.97−1.04	.74	**0.93**	**0.89−0.97**	**<.001**
Male sex	0.85	0.49−1.47	.57	0.89	0.49−1.61	.70
Age	1.0	0.97−1.02	.73	1.0	0.98−1.02	.97
Model 2	Achieving IHS4 category change					
Adalimumab	**1.69**	**1.00−2.86**	**.05**	**2.91**	**1.75−4.92**	**<.001**
Hurley stage 3	**0.52**	**0.30−0.88**	**.02**	**0.57**	**0.33−0.95**	**.03**
Family history	1.02	0.55−1.86	.96	1.25	0.70−2.22	.45
Current smoker	0.82	0.48−1.39	.45	1.01	0.58−1.76	.97
Antibiotic use	—	—	—	0.76	0.39−1.47	.42
BMI	1.02	0.99−1.06	.22	**0.95**	**0.91−0.98**	**.006**
Male sex	0.73	0.41−1.29	.29	**0.55**	**0.31−0.96**	**.04**
Age	1.0	0.98−1.02	.94	0.99	0.97−1.02	.63

BMI, Body mass index; *CI*, confidence interval; *HiSCR*, hidradenitis suppurativa clinical response; *IHS4*, International Hidradenitis Suppurativa Severity Score; —, not applicable.

with a 39.79% reduction in IHS4 score in adjusted analysis (b = −39.79; 95% CI −54.92 to −24.65; $P < .001$). Each unit increase in BMI (as a continuous variable) attenuated the percentage change in IHS4 score by 1.65% (b = 1.65; 95% CI 0.50-2.81; $P = .01$). No other significant covariates were identified.

DISCUSSION

The effect of substituting HiSCR with IHS4 as the primary outcome measure of the PIONEER phase 3 clinical trials depended on whether the outcome variable was binary or continuous. Substituting HiSCR with change in IHS4 category resulted in no statistically significant difference between adalimumab and placebo in PIONEER 1 (Table II). Continuous variables (both nodule counts and IHS4 values) were statistically significant in both studies. Integrating draining tunnel status (using the IHS4) reduced placebo response rates in both PIONEER 1 and 2 regardless of whether a binary or continuous

Table IV. Linear regression model of change in nodules (model 1) and % change in International Hidradenitis Suppurativa Severity Score outcome measure (model 2) in adalimumab-treated patients in PIONEER 1 and PIONEER 2

	PIONEER 1			PIONEER 2		
Variable	**Estimate**	**95% CI**	***P* value**	**Estimate**	**95% CI**	***P* value**
Model 1			Change in nodules			
Adalimumab	**−2.36**	**(−4.40 to −0.31)**	**.02**	**−2.58**	**(−3.97 to −1.19)**	**<.001**
Hurley stage 3	**2.23**	**(−0.01 to 4.48)**	**.05**	−0.17	(−1.63 to 1.29)	.82
Family history	−0.74	(−3.19 to 1.72)	.56	−0.59	(−2.17 to 0.99)	.47
Current smoker	−1.00	(−3.08 to 1.08)	.35	−0.05	(−1.56 to 1.46)	.94
Presence of draining tunnels	1.09	(−1.49 to 3.66)	.41	**1.87**	**(0.32 to 3.43)**	**.02**
Antibiotic use	—	—	—	1.10	(−0.67 to 2.88)	.22
BMI	−0.04	(−0.18 to 0.09)	.54	−0.01	(−0.11 to 0.10)	.89
Male sex	−0.46	(−2.67 to 1.75)	.68	0.02	(−1.55 to 1.60)	.98
Age	0.03	(−0.06 to 0.12)	.51	0.03	(−0.03 to 0.09)	.38
Model 2			% Change in IHS4			
Adalimumab	**−18.60**	**(−33.64 to −3.55)**	**.02**	**−39.79**	**(−54.92 to −24.67)**	**<.001**
Hurley stage 3	8.45	(−6.89 to 23.80)	.28	2.54	(−12.83 to 17.90)	.75
Family history	−3.61	(−21.50 to 14.28)	.69	−6.59	(−23.77 to 10.59)	.45
Current smoker	1.29	(−14.04 to 16.63)	.87	4.68	(−11.71 to 21.07)	.57
Antibiotic use	—	—	—	16.75	(−2.52 to 36.02)	.09
BMI	0.17	(−0.82 to 1.15)	.74	**1.65**	**(0.50 to 2.81)**	**.01**
Male sex	10.61	(−5.52 to 26.75)	.20	8.82	(−7.70 to 25.34)	.29
Age	0.27	(−0.40 to 0.94)	.43	−0.04	(−0.72 to 0.65)	.92

BMI, Body mass index; *IHS4*, International Hidradenitis Suppurativa Severity Score.

variable was used. The use of the IHS4 as a continuous variable resulted in placebo response rates consistent with those of studies of psoriasis and atopic dermatitis (4.5%-12%).[10-13] This suggests that the placebo response rate is partially a product of the HiSCR outcome measure (ie, the use of a binary outcome), as well as the natural variability of inflammatory lesions in hidradenitis suppurativa and interrater variation in counting lesions.[3] It is recognized that the use of dichotomous outcomes reduces the power to detect difference between groups, increases the risks of false-positive results, and subsumes the variability in response within a group or cohort.[14] Because the IHS4 score is weighted toward abscesses and draining tunnels as opposed to nodules, it can be hypothesized that tunnels are less susceptible to such variability compared with superficial nodules, and hence the resolution of drainage is more indicative of successful therapy. The interrater variability of counting nodules has been previously identified as a factor contributing to placebo response rates,[3] and recent proposals for outcome measures assessing disease severity that do not include counts may provide a novel approach once validated in larger cohorts.[15] The association of elevated placebo response rates with specific outcome measures is an important finding, given the recent nonsignificant results of clinical trials evaluating C5a antagonists in hidradenitis suppurativa.[3,10] A recent phase 2b trial concluded that IFX-1 (InflaRx, Jena, Germany) was nonsuperior to placebo as measured by the HiSCR, with a placebo response rate of 47.2%. Post hoc analysis identified a significant reduction in draining tunnels compared with placebo as well as quality-of-life outcomes.[10]

Severe disease (assessed by the presence of draining tunnels) was significantly associated with a reduction in achieving HiSCR in PIONEER 2 (Table III), and Hurley stage 3 disease was associated with reduced odds of achieving IHS4 category change (Table III). In linear regression modeling, Hurley stage 3 disease was associated with an altered mean change in nodule count in PIONEER 1, and draining tunnels were associated with an altered mean change in nodule count in PIONEER 2. These results are consistent with the fact that severe disease (manifested either in increased Hurley staging or presence of draining tunnels) is less responsive to adalimumab therapy. BMI was significant in reducing HiSCR achievement, IHS4 category improvement, and percentage change in IHS4 in PIONEER 2. Every unit increase in BMI decreased the OR of achieving HiSCR by 7.1%, IHS4 category improvement by 4.9%, and the percentage change in IHS4 by 1.57%. The possibility of weight-based responses to current dosages of adalimumab in hidradenitis suppurativa requires further

investigation. Smoking is known to affect the efficacy of adalimumab in Crohn's disease,[16] and this is mirrored in hidradenitis suppurativa with our results (Table III, PIONEER 2 HiSCR).

The presence of any draining tunnels was significantly associated with HiSCR in PIONEER 2 but was not significantly different between adalimumab and placebo groups (Table I). Therefore, we conclude that draining tunnels is not a confounder on the effect of adalimumab in hidradenitis suppurativa but does have a significant association with HiSCR and change in nodule counts. The discrepancies in results between PIONEER 1 and 2 studies may be attributable to statistically significant differences in baseline patient characteristics (Supplemental Table I; available at https://doi.org/10.17632/7jmyytrzyx.1. Statistically significant differences were observed in race, age, BMI, smoking status, and presence of draining tunnel, and the median nodule and draining tunnel counts were significantly lower in PIONEER 2 compared with PIONEER 1. Additionally, baseline IHS4 scores were higher in PIONEER 1, indicating patients had more severe disease in PIONEER 1 than PIONEER 2.

The results of our analysis concur with those of Kimball et al[2] in that draining tunnels are not a confounder on the effect of adalimumab in hidradenitis suppurativa. However, our results go farther in identifying that draining tunnels, smoking status, antibiotic use, and BMI have an effect on clinical response as measured by HiSCR. These effects were more prominent in PIONEER 2 in the presence of less severe disease, suggesting they may influence response to adalimumab in patients with a disease severity similar to that of those included in PIONEER 2. Using an outcome measure that integrates draining tunnels (IHS4) identifies individuals with Hurley stage 3 disease as having reduced odds of achieving a change in IHS4 severity category compared with those with Hurley stage 2 disease. Stage 3 patients also exhibited a decreased change in nodule counts in the setting of adalimumab therapy compared with placebo. This suggests that despite the recent discussion in regard to the lack of biological correlation between Hurley staging and disease severity,[17] Hurley stage 3 disease has a statistically significant effect on the reduction of nodules in the setting of adalimumab therapy.

The limitations of this study include the inherent limitations of using clinical trial data, with the PIONEER studies not being an accurate representation of actual clinical practice. They also exclude the most severe cases of hidradenitis suppurativa, given that more than 20 draining tunnels was an exclusion criterion. Additionally, the data analyzed included only 12 weeks of therapy, but independent analysis suggests that response at week 12 is associated with clinical response at week 36 of therapy.[18]

The potential clinical applications of our findings are immediate in that treatment with adalimumab before the development of draining tunnels and Hurley stage 3 disease may be more efficacious. The statistically significant association with BMI also suggests that patients with increased BMI may have a decreased clinical response to adalimumab; however, it is unclear whether the degree of change (Tables III and IV) reaches clinical significance. Further investigation into the weight-based response to adalimumab in hidradenitis suppurativa is warranted, given these preliminary findings.

CONCLUSIONS

Adalimumab 40 mg weekly is effective in reducing clinical disease activity as measured by both the HiSCR and the IHS4 compared with placebo in participants with hidradenitis suppurativa. High placebo response rates may be a product of the use of binary outcome measures such as HiSCR. Regression analyses identified draining tunnels, smoking, antibiotic use, and BMI as independent significant associations with clinical response to adalimumab as measured by HiSCR in PIONEER 2. Only BMI was significantly associated with the use of percentage change in IHS4 in PIONEER 2. Future placebo-controlled studies of novel therapies in hidradenitis suppurativa should acknowledge the influence of outcome measure in the interpretation of their data.

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