Adalimumab in conjunction with surgery compared with adalimumab monotherapy for hidradenitis suppurativa: A Randomized Controlled Trial in a real-world setting

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Background: Adalimumab, the only biologic registered for hidradenitis suppurativa, shows clinical response in up to 60% of patients, leaving many patients in need for other treatment options such as surgery.

Objective: To compare the clinical effectiveness of adalimumab combined with surgery vs adalimumab monotherapy in patients with moderate to severe hidradenitis suppurativa.

Methods: A pragmatic Randomized Controlled Trial was performed from August 2018 to July 2022. Primary outcome was the difference in mean International Hidradenitis Suppurativa Severity Score System reduction after 12 months of treatment with the difference in mean Dermatology Life Quality Index reduction as a key secondary outcome.

Results: Thirty-one patients were included per arm. The mean International Hidradenitis Suppurativa Severity Score System at baseline was 23.9 ± 10.7 in the surgery group and 20.9 ± 16.4, in the monotherapy group. After 12 months of treatment the surgery group had a significantly greater reduction in International Hidradenitis Suppurativa Severity Score System compared with the monotherapy group (−19.1 ± 11.3 vs −7.8 ± 11.8, $P < .001$). Moreover, the surgery group showed a greater reduction in Dermatology Life Quality Index after treatment compared with the monotherapy group (−8.2 ± 6.2 vs −4 ± 7.7, $P = .02$).

Limitations: The study follow-up was too short to assess surgical recurrence rates.

Discussion: Combining adalimumab with surgery resulted in greater clinical effectiveness and improved quality of life after 12 months in patients with moderate to severe hidradenitis suppurativa. (J Am Acad Dermatol 2023;89:677-84.)

Key words: adalimumab; biologics; hidradenitis suppurativa; quality of life; surgery.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin disease. The disease is characterized by inflammatory nodules, abscesses, and draining tunnels occurring most commonly in the axillary, inguinal, and anogenital regions.[1] HS-associated pain, pruritus, malodor, and suppuration are known to greatly reduce the quality of life of patients.[2]

While the treatment of HS has improved over recent years with the registration of adalimumab for HS, this treatment still only shows a response in up to 60% of patients measured using the Hidradenitis Suppurativa Clinical Response (HiSCR) in the first Randomized Controlled Trials (RCTs). While reducing inflammatory nodules and abscesses, data derived from the PIONEER studies showed that the number of draining tunnels only marginally improved during adalimumab treatment.[3-5] This likely explains why in real-world adalimumab studies most patients (>70%) require surgery in addition to their biologic therapy and HiSCR response rates are markedly higher than in the RCTs (60% vs 70%).[6,7] These chronic lesions are known to flare or recur when adalimumab treatment is discontinued. These data suggest that adalimumab monotherapy is insufficient in reducing the disease burden in many patients with HS and additional therapeutic measures are required.

Surgery (deroofing, limited or wide excision) is frequently used as additional therapy in clinical practice. However, the added value of surgical intervention during adalimumab treatment has not yet been investigated in a controlled study.[8-10] Although concerns have been raised about the safety of continuation of biologics around and during surgery a recent RCT clearly demonstrated that adalimumab treatment did not result in increased peri-surgical adverse events (AEs), proving that anti-tumor necrosis factor therapy does not need to be interrupted around surgery in patients with HS.[11]

In this study, we aimed to compare the real-world effectiveness of adalimumab and adjuvant surgery with adalimumab monotherapy in patients with moderate to (very) severe HS within the context of a pragmatic, phase IV RCT.

CAPSULE SUMMARY

- Evidence for the combination of adalimumab with surgery is scarce. This study shows superior clinical and patient reported outcomes when surgery is combined with adalimumab.
- Adalimumab should always be proposed in combination with surgery to patients with moderate to severe hidradenitis suppurativa.

METHODS

Study design

This pragmatic, phase IV RCT (NCT03221621) was conducted at the Department of Dermatology of the Erasmus University Medical Center Rotterdam, The Netherlands from August 2018 to July 2022. Patients were randomized to either adalimumab with surgery or adalimumab monotherapy in a 1:1 ratio in blocks of 6 using a computer randomization program. Both treatment groups received adalimumab (40 mg once weekly) for 12 months and visited the hospital every 3 months (Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/8kbhfctrgj/1). The surgery group additionally received a maximum of 2 surgical interventions (eg, deroofing, limited or wide excision) after 3 months.[12,13] The monotherapy group was offered the option to cross-over to the surgical group when HiSCR was not achieved after 6 months of treatment. Patients who dropped out before week 12 were replaced.

Participants

Adult patients with moderate to severe HS, according to the Hidradenitis Suppurativa Physician's Global Assessment scale,[14] were eligible for inclusion. Exclusion criteria included oral antibiotics within 2 weeks, oral corticosteroids within 4 weeks, and biologics within 5 half-lives prior to baseline. All in- and exclusion criteria, including allowed rescue therapy are reported in the supplemental methods.

Assessments

The primary outcome measure was the difference in International Hidradenitis Suppurativa Severity Score System reduction between the groups at the end of treatment (12-month visit or last visit before discontinuation; last observation carried forward).[15] Secondary outcome measures included the difference in change in: Dermatology Life Quality Index,[16] abscess and inflammatory nodule (AN) count, and draining tunnel between groups. Additionally, we measured the percentage of patients who achieved HiSCR (≥50% reduction in AN-count, no increase of abscesses, and no increase of draining fistulas),[17]

Abbreviations used:

AE: adverse event
AN: abscess and inflammatory nodule
HiSCR: Hidradenitis Suppurativa Clinical Response
HS: hidradenitis suppurativa
IHS4: International Hidradenitis Suppurativa Severity Score System
RCT: Randomized Controlled Trial

International Hidradenitis Suppurativa Severity Score System (IHS4)-55[18] (55% reduction in IHS4 score), a ≥2 point difference in the Hidradenitis Suppurativa Physician's Global Assessment scale, and a ≥2 point change on a 5-point pain rating scale. Patient satisfaction was measured at the end of treatment on a 5-point scale and compared between the 2 groups. Adverse events were recorded from screening through the end of the study. Recurrence was evaluated at every visit after surgery and defined as: the occurrence of an inflammatory lesion within 5 mm from the surgical border. The global scheme of assessments is illustrated in Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/8kbhfctrgj/1.

Statistical analysis

Sample size calculation indicated that 31 patients per arm would result in a power of 80% to prove a difference of 35.11% in International Hidradenitis Suppurativa Severity Score System reduction (Supplementary Methods). An intention to treat analysis was performed to assess the difference between treatment strategies. For patients who discontinued the study prior to 12 months, the last visit before discontinuation was regarded as the endpoint of treatment (last observation carried forward) and a non-responder imputation analysis was performed on the dichotomous IHS4 (IHS4-55). In addition, to account for patients who crossed over between groups an additional per protocol sensitivity analysis was performed.

Baseline characteristics are presented as mean ± SD or *n* (%). For continuous variables, the normality was assessed prior to further analysis using the histogram and Shapiro-Wilk test. Differences between groups were analyzed using an independent *t* test or a Mann-Whitney U test, where appropriate. For categorical variables, differences between groups were assessed using a χ^2 test or Fisher's Exact. All comparisons were 2-sided and *P* values ≤.05 were considered statistically significant. Statistical analyses were performed in SPSS Statistics 28.0 (IBM Corporation).

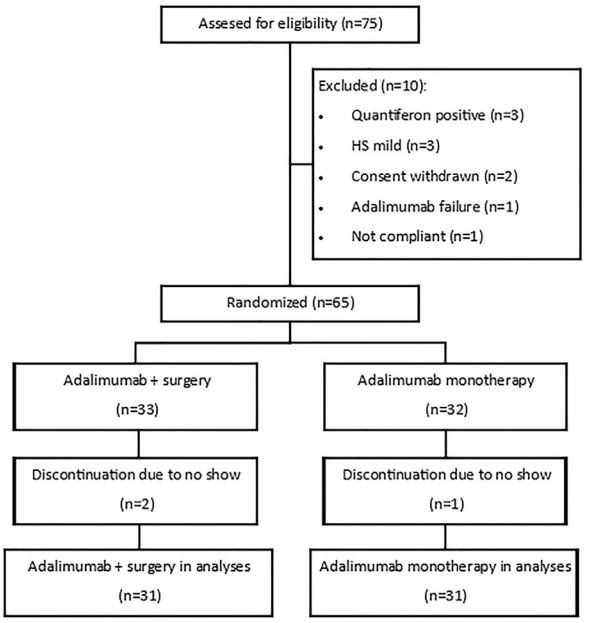

Fig 1. Flowchart of patient inclusion.

Ethics

The protocol was reviewed and approved by the local medical ethical review board (MEC-2016-680) and the study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. All patients provided written informed consent before enrollment.

RESULTS

Study participants

Seventy-five patients were screened and 65 patients were randomized. This included 3 replacements (1 in monotherapy group and 2 in surgery group) for patients who discontinued before week 12. A flowchart of the inclusion process is shown in Fig 1. There were no significant differences in baseline characteristics between the 2 treatment groups (Table I).

Three patients (10%) from the monotherapy group crossed over after 6 months and underwent surgery. In the surgery group 26 patients received a total of 37 surgeries. Of this group, 4 patients (13%) discontinued before month 6 resulting in an endpoint without receiving surgery and 1 patient withdrew consent for surgery (3%). In total, 13 (21%) patients discontinued before 12 months, 6 (19%) in the surgery group and 7 (23%) in the monotherapy group. In the surgery group, 4 patients were lost to follow-up, 1 requested discontinuation due to remission, and 1 patient discontinued due to an AE not related to treatment.

Table I. Patient characteristics

Patient characteristics	ADA + surgery (*n* = 31)	ADA monotherapy (*n* = 31)
Age, mean ± SD	40.2 ± 11.7	37.5 ± 12.7
Sex*, *n* (%)	17 (55)	17 (55)
Body mass index, mean ± SD	29.5 ± 6.6	30.2 ± 6.1
Disease duration (y), mean ± SD	17 ± 8.7	14.7 ± 10.5
Family history, *n* (%)	16 (52)	14 (45)
Current or ex-smoker, *n* (%)	27 (87)	24 (77)
IHS4-score, mean ± SD	23.9 ± 10.7	20.9 ± 16.4
Mild, *n* (%)	0 (0)	1 (3)
Moderate, *n* (%)	4 (13)	10 (32)
Severe, *n* (%)	27 (87)	20 (65)
Hurley stage, *n* (%)		
Hurley stage I	1 (3)	1 (3)
Hurley stage II	22 (71)	22 (71)
Hurley stage III	8 (26)	8 (26)
Refined Hurley stage, *n* (%)		
Mild (1A, 2A)	0 (0)	1 (3)
Moderate (1B, 2B)	7 (23)	12 (39)
Severe (1C, 2C, 3)	24 (77)	18 (58)
HS-PGA, *n* (%)		
Mild	0 (0)	1 (3)
Moderate	15 (48)	18 (58)
Severe	3 (10)	2 (7)
Very severe	13 (42)	10 (32)
DLQI, mean ± SD	16.2 ± 6.4	16.0 ± 6.0
Lesion count, mean ± SD		
Inflammatory nodules	3.6 ± 4.0	3.5 ± 3.8
Abscesses	0.7 ± 1.1	0.3 ± 0.6
Draining tunnels	4.7 ± 2.9	4.2 ± 4.3
AN-count	4.3 ± 4.3	3.8 ± 3.9

ADA, Adalimumab; *AN-count*, abscess and inflammatory nodule count; *DLQI*, Dermatology Life Quality Index; *HS-PGA*, Hidradenitis Suppurativa Physician's Global Assessment scale; *IHS4*, International Hidradenitis Suppurativa Severity Score System.
*Female.

In the monotherapy group, 3 patients discontinued due to AEs related to treatment, 2 patients on patient request, and 2 patients due to an active pregnancy wish. Furthermore, 15 (48%) patients of the monotherapy group required rescue therapy compared with 9 (29%) in the surgery group (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/8kbhfctrgj/1).

Effectiveness

The surgery group showed a greater decrease in IHS4 at the end of treatment compared with the monotherapy group, −19.1 ± 11.3 vs −7.8 ± 11.8 ($P < .001$), respectively (intention to treat analysis). The difference in International Hidradenitis Suppurativa Severity Score System over time is shown in Fig 2.

At the end of treatment, more patients in the surgery group achieved a ≥2 point change in Hidradenitis Suppurativa Physician's Global Assessment scale (58%, 18/31) compared with the monotherapy group (18%, 4/31), $P < .001$. There was no significant difference in the mean change in AN-count between the 2 groups (Table II). However, draining tunnels showed a greater reduction in the surgery group, with a mean reduction of −4.1 ± 3 and −1.6 ± 3, $P = .002$, for the surgery group and monotherapy group, respectively.

There was no difference in the percentage of patients that achieved HiSCR between both groups (59% and 38% respectively, $P = .22$). However, patients in the surgery group (87% vs 32%, $P < .001$) achieved IHS4-55 significantly more often than the patients in the monotherapy group. This result remained after non-responder imputation (81% vs 19%, $P < .001$). The overall short-term recurrence rate after surgery was 10% ($n = 4/31$, Supplementary Table I).

Patient reported outcome measures

In line with the physician reported outcomes, the surgery group showed a greater improvement in

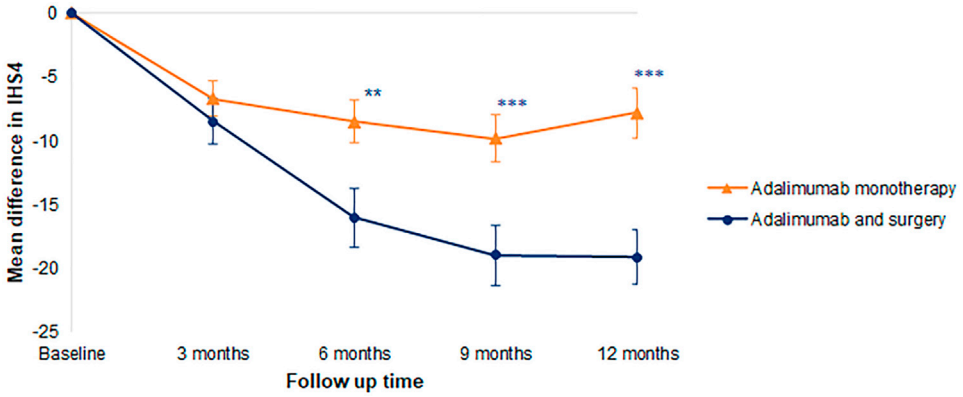

Fig 2. The difference in International Hidradenitis Suppurativa Severity Score System over time. Illustrated in mean with SE. $^{**}P < .01$ $^{***}P < .001$. *IHS4*, International Hidradenitis Suppurativa Severity Score System.

Table II. Clinical and patient reported outcomes after 12 months of treatment

	ADA + surgery (N = 31)	ADA monotherapy (N = 31)	P value
ΔIHS4, mean ± SD	−19.1 ± 11.3	−7.8 ± 11.8	**<.001**
IHS4-55, *n* (%)	27 (87)	10 (32)	**<.001**
≥2 change in HS-PGA, *n* (%)	18 (58)	4 (13)	**<.001**
ΔAN-count, mean ± SD	−2.4 ± 3.2	−1.4 ± 3.5	.24
HiSCR, *n* (%)	10 (59)*	6 (38)*	.22
ΔDraining tunnels, mean ± SD	−4.1 ± 3	−1.6 ± 3	**.002**
ΔDLQI, mean ± SD	−8.2 ± 6.2	−4 ± 7.7	**.02**
≥2 change in pain, *n* (%)	8 (27)	3 (10)	.09
Patient satisfied, *n* (%)	25 (93)*	15 (65)*	**.02**

Significant values are shown in bold.
ADA, Adalimumab; *ΔAN-count*, difference in change in abscess and inflammatory nodule count; *ΔDLQI*, difference in change in Dermatology Life Quality Index; *HiSCR*, Hidradenitis Suppurativa Clinical Response; *HS-PGA*, Hidradenitis Suppurativa Physician's Global Assessment scale; *ΔIHS4*, difference in International Hidradenitis Suppurativa Severity Score.
*Missing values; HiSCR: 14 in surgery group and 15 in monotherapy group; patient satisfaction: 4 in surgery group and 8 in monotherapy group.

Dermatology Life Quality Index at the end of treatment compared with the monotherapy group, −8.2 ± 6.2 and −4 ± 7.7, P = .02, respectively (Fig 3). At the end of treatment, only the surgery group showed a significant decrease in pain score (P = .044, monotherapy group P = .103). Comparison between the 2 groups, however, only showed a trend in favor of the surgery group (27%, 8/31 vs 10%, 3/31, P = .09). Overall, patients in the surgery group (93%, 5/27) were more satisfied with the treatment strategy than those in the monotherapy group (65%, 15/23), P = .02. Furthermore, a total of 22 (71%) patients from the adalimumab monotherapy group opted for surgery during or within 3 months after study completion.

All significant clinical and patient reported outcome measures remained significant in the per protocol analysis (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/8kbhfctrgj/1).

Safety

Adverse events were reported in 29 (94%) patients of the monotherapy group compared with 21 (68%) patients in the surgery group (P = .01). In total, 79 AEs were reported in the monotherapy group and 49 in the surgery group, from which 58 (73%) and 36 (73%) were potentially related to treatment, respectively. The most common AEs potentially related to treatment were: HS flares, viral/bacterial infections (eg, urinary tract infections and tonsillitis), hematoma at the injection site, mild bleeding of the surgical site, and postoperative pain. In the monotherapy group, a HS flare was reported 27 (35%) times, versus 11 (22%) times in the surgery group. Nine (12%) infections occurred in the monotherapy group versus 6 (12%) in the surgery group of which urinary tract infections occurred most often (4 in the monotherapy and 3 in the surgery group), followed by tonsillitis (2 vs 0).

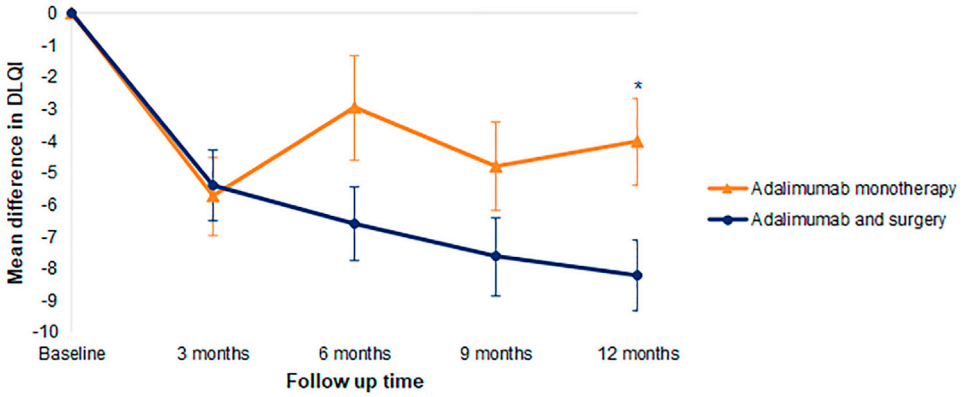

Fig 3. The difference in change in Dermatology Life Quality Index over time. Illustrated in mean with SE. *$P < .05$. *DLQI*, Dermatology Life Quality IndexDermatology Life Quality Index.

In both groups, 2 severe adverse events (SAEs) occurred. In the monotherapy group, 1 patient developed cancer of the urinary tract and 1 patient was hospitalized due to a noninfectious fever. In the surgery group a non−ST-elevation myocardial infarction and a minor stroke occurred. All SEAs were ultimately deemed unrelated to the study interventions (either adalimumab or surgery) by treating physicians. A detailed overview of the SAEs is shown in Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/8kbhfctrgj/1.

DISCUSSION

This RCT investigated the effectiveness of combining surgery with adalimumab and adalimumab monotherapy in patients with moderate to severe HS. Combining adalimumab with surgery resulted in a significantly greater clinical response and a significantly improved quality of life compared with adalimumab monotherapy after 12 months.

Our results are in line with previously published data showing that the greatest clinical response to adalimumab is achieved after 3 months of treatment (Fig 2).[19] Nonetheless, in the monotherapy group a significant proportion of inflammatory lesions persisted after this time point, supporting the need for additional surgery.[3] In our study, the benefit of additional surgery was striking, with significant reductions in IHS4 score as well as patient's quality of life. This also confirms previous findings of a observational study which showed a faster decline in the disease activity scores after a combination of adalimumab and surgery compared with biologic monotherapy or surgery monotherapy.[20]

In our pragmatic real-world study, patients had a relatively low AN-count but frequently presented with multiple draining tunnels at baseline, >95% of patients had at least 1 draining tunnel. This is high compared to the PIONEER studies where the prevalence of draining tunnels ranged from 62% to 75%.[21] As the presence of draining tunnels is associated with a prolonged time to achieve HiSCR this fact could explain the lower HiSCR rates in our study (38%) compared with long-term data of the PIONEER studies (58%).[19,22]

The PIONEER studies also showed that, despite its beneficial effects in suppressing recurrent nodules and abscesses, adalimumab does not have the therapeutic potential to induce full remission of draining tunnels.[3] We argue that full remission should be pursued, because residual skin inflammation might stimulate systemic inflammation and as such can trigger the formation of new lesions. This view is based on the observation that epithelialized tunnels are associated with increased infiltration of immune cells forming a major source of inflammation.[23] During surgery, the highly inflammatory tunnels are removed, reducing the overall inflammatory load, enhancing the effectiveness of adalimumab, and increasing the chance for a patient to achieve remission.

However, recurrences can still occur after surgery and our study showed a recurrence rate of 10% consistent with current literature.[24] Taking these recurrences into account, more patients in the monotherapy had at least 1 AE compared with the surgery group (P = .01). Most prominently, acute flares were more frequently seen in the monotherapy group (27 vs 11) where AEs not related to treatment (21 vs 13) were more frequent in the surgery group, respectively. It should be noted that several SAEs occurred (6%) during the study, which is relatively high but can be explained by the pragmatic nature of this study.

Pain is a prominent symptom of HS and a reduction in pain is an important outcome measure in HS. While a significant reduction in pain score was seen in the surgery group and not in the monotherapy

group, the difference between the 2 groups was not significant. This may be related to the use of a 5-point pain scale, which is less sensitive than NRS of pain with a 10-point Likert-scale. Nonetheless, the significant improvement of pain scores in the surgery group might even be underrated as the COVID-19 pandemic forced us to be more flexible with the planning of the surgeries. Therefore, the time between surgery and the next follow-up visit might have been insufficient to overcome the discomfort of the post-surgical wound itself.

This study has a few limitations. We had a relatively high rate of patients who discontinued before 12 months. However, taking these lost-to-follow-up patients into account using non-responder imputation, the surgery group still demonstrated a significantly greater reduction in IHS4-55 than the monotherapy group. In addition, a longer follow-up would provide better insights in the maintenance of disease control and also the prevalence of recurrences after surgery.

Nonetheless, an important strength of this study is that it resembles the real-world practice, with a representative visit frequency, broad inclusion criteria, clinically relevant outcome measures, and an intention to treat analysis.

CONCLUSION

This pragmatic RCT investigated the clinical effect of combining surgery with adalimumab treatment. The combination of adalimumab with surgery showed significantly greater clinical effectiveness and improvement in quality of life than adalimumab monotherapy with a higher rate of patient satisfaction. The therapeutic option of adalimumab with surgery should always be proposed to patients with moderate to severe HS.

Conflicts of interest

None disclosed.

REFERENCES

1. Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers*. 2020;6:18.
2. Montero-Vilchez T, Diaz-Calvillo P, Rodriguez-Pozo JA, et al. The burden of hidradenitis suppurativa signs and symptoms in quality of life: systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021;18:6709.
3. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016;375:422-434.
4. Orita A, Kitamura S, Maeda T, et al. Hidradenitis suppurativa successfully treated with two-stage surgery under disease control with adalimumab. *J Dermatol*. 2022;49:e1-e2.
5. Saito-Sasaki N, Sawada Y, Sato S, et al. Possible beneficial impact of surgical deroofing procedure to cover the disadvantage of adalimumab treatment for hidradenitis suppurativa. *J Dermatol*. 2022;49:e3-e4.
6. Gulliver W, Alavi A, Wiseman MC, et al. Real-world effectiveness of adalimumab in patients with moderate-to-severe hidradenitis suppurativa: the 1-year SOLACE study. *J Eur Acad Dermatol Venereol*. 2021;35:2431-2439.
7. Hafner A, Ghislain PD, Kovács R, et al. Improvement in Hidradenitis suppurativa and quality of life in patients treated with adalimumab: real-world results from the HARMONY Study. *J Eur Acad Dermatol Venereol*. 2021;35:2277-2284.
8. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29:619-644.
9. Aarts P, Dudink K, Vossen A, et al. Clinical implementation of biologics and small molecules in the treatment of hidradenitis suppurativa. *Drugs*. 2021;81:1397-1410.
10. Wollina U, Brzezinski P, Koch A, Philipp-Dormston WG. Immunomodulatory drugs alone and adjuvant to surgery for hidradenitis suppurativa/acne inversa-A narrative review. *Dermatol Ther*. 2020;33:e13877.
11. Bechara FG, Podda M, Prens EP, et al. Efficacy and safety of adalimumab in conjunction with surgery in moderate to severe hidradenitis suppurativa: the SHARPS Randomized Clinical Trial. *JAMA Surg*. 2021;156:1001-1009.
12. van der Zee HH, Prens EP, Boer J. Deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. *J Am Acad Dermatol*. 2010;63:475-480.
13. Shavit E, Pawliwec A, Alavi A, George R. The surgeon's perspective: a retrospective study of wide local excisions taken to healthy subcutaneous fat in the management of advanced hidradenitis suppurativa. *Can J Surg*. 2020;63:E94-E99.
14. Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. *Dermatology*. 2015;231:184-190.
15. Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol*. 2017;177:1401-1409.
16. Gergely LH, Gáspár K, Brodszky V, et al. Validity of EQ-5D-5L, Skindex-16, DLQI and DLQI-R in patients with hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2020;34:2584-2592.
17. Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol*. 2014;171:1434-1442.
18. Tzellos T, van Straalen KR, Kyrgidis A, et al. Development and validation of IHS4-55, an IHS4 dichotomous outcome to assess treatment effect for hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2022;37:395-401.
19. Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. 2019;80:60-69.e2.
20. Shanmugam VK, Mulani S, McNish S, Harris S, Buescher T, Amdur R. Longitudinal observational study of hidradenitis suppurativa: impact of surgical intervention with adjunctive biologic therapy. *Int J Dermatol*. 2018;57:62-69.
21. Frew JW, Jiang CS, Singh N, et al. 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. *J Am Acad Dermatol*. 2020;82:1150-1157.
22. Frew JW, Jiang CS, Singh N, et al. Dermal tunnels influence time to clinical response and family history influences time to

loss of clinical response in patients with hidradenitis suppurativa treated with adalimumab. *Clin Exp Dermatol*. 2021;46:306-313.

23. Navrazhina K, Frew JW, Gilleaudeau P, Sullivan-Whalen M, Garcet S, Krueger JG. Epithelialized tunnels are a source of inflammation in hidradenitis suppurativa. *J Allergy Clin Immunol*. 2021;147:2213-2224.
24. Riddle A, Westerkam L, Feltner C, Sayed C. Current surgical management of hidradenitis suppurativa: a systematic review and meta-analysis. *Dermatol Surg*. 2021;47:349-354.