Apremilast for moderate hidradenitis suppurativa: results of a randomised controlled trial

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ABSTRACT

Background

Effective anti-inflammatory treatments for hidradenitis suppurativa (HS) are limited.

Objective

To evaluate the efficacy and short-term safety of apremilast in patients with moderate HS.

Methods

A total of 20 patients with moderate HS were randomised in a 3 : 1 ratio to receive blinded treatment with apremilast, 30 mg twice daily, or placebo for 16 weeks. The primary outcome was the Hidradenitis Suppurativa Clinical Response at week 16. Linear mixed effects modelling (analysis of covariance) was used to assess secondary clinical outcomes between treatment groups.

Results

The Hidradenitis Suppurativa Clinical Response was met in 8 of 15 patients in the apremilast group (53.3%) and none of 5 patients in the placebo group (0%) (p = 0.055) at week 16. Moreover, the apremilast-treated patients showed a significantly lower abscess and nodule count (mean difference, −2.6; 95% confidence interval, −6.0 to −0.9; p = 0.011), NRS for pain (mean difference, −2.7; 95% confidence interval, −4.5 to −0.9; p = 0.009), and itch (mean difference, −2.8; 95% confidence interval, −5.0 to −0.6; p = 0.015) over 16 weeks compared with the placebo-treated patients. There was no significant difference in the Dermatology Life Quality Index over time between the 2 treatment groups (mean difference, −3.4; 95% confidence interval, −9.0 to 2.3; p = 0.230). The most frequently reported adverse events in the apremilast-treated patients were mild-to-moderate headache and gastrointestinal symptoms, which did not result in dropouts.

Limitations

Small number of patients, relatively short study duration.

Conclusion

Apremilast, at a dose of 30 mg twice daily, demonstrated clinically meaningful efficacy and was generally well tolerated in patients with moderate HS.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, recurrent, autoinflammatory skin disorder with an estimated prevalence of approximately 1% of the general population.[1] The disease occurs more frequently in females and usually presents during adolescence with painful, itchy, deep-seated, inflamed nodules, abscesses, and sinus tracts predominantly in the axillae and inguinal and anogenital regions.[1,2] Disease severity can be categorised into 6 stages, ranging from clear (stage 0) to very severe (stage 6) according to the Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA).[3] HS may progress over time, supporting the need for early intervention.

Currently, first-line therapies for moderate HS include anti-inflammatory oral antibiotics such as the tetracyclines and the combination of clindamycin and rifampicin.[4] Second-line treatment includes adalimumab, which is the only registered treatment for moderate-to-severe HS that provides clinically meaningful improvements.[5] Other biologic therapies have not been extensively studied in patients who have HS or are currently in the early stages of its clinical development.[6] Taken together, the high-quality evidence on HS treatment is limited, highlighting a significant unmet need for novel effective anti-inflammatory therapies.

Recently, in a small case series, 5 of 6 patients with moderate-to-severe HS treated with apremilast, 30 mg twice daily for 3 months, showed a promising response.[7] In addition, the clinical efficacy of apremilast for patients with moderate-to-severe psoriasis and psoriatic arthritis has previously been proved in multiple clinical trials.[8-10] Apremilast is an orally administered small molecule drug that specifically inhibits phosphodiesterase 4 and modulates the expression of a variety of proinflammatory and anti-inflammatory mediators.[11-13] As apremilast targets phosphodiesterase 4 in several inflammatory cell types involved in the pathogenesis of HS, such as T cells, natural killer cells, neutrophils, monocytes, and dendritic cells, we hypothesised that it might have a beneficial effect in patients with HS.

The objective of this double-blind randomised placebo-controlled trial was to investigate the clinical efficacy and short-term safety and tolerability of apremilast in patients with moderate HS. We specifically chose a study population with moderate HS because the clinical efficacy of apremilast in psoriasis (as measured by reaching a 90% improvement in baseline Psoriasis Area Severity Index score) is lower than that of most anti-tumour necrosis factor-α agents and certainly lower than that of the recently introduced anti-interleukin 17 agents and anti-interleukin 23p19 biologics.[14]

MATERIALS AND METHODS

Patients

Patients who were at least 18 years of age with moderate HS, defined as a HS-PGA score of 3, were enrolled. Additionally, patients were required to have at least 4 inflammatory lesions (i.e. abscesses, draining sinuses/tunnels, or inflammatory nodules in at least 2 anatomic locations). Patients receiving systemic antibiotics or immunosuppressive and/or immunomodulating therapy were required to stop treatment at least 28 days before baseline and until the end of study. Patients were excluded if they had minimal, mild, severe, or very severe disease severity according to the HS-PGA scale; any clinically significant active systemic disease or infection; a diagnosis of or suspected Crohn's disease; a history of major psychiatric illness requiring hospitalisation within the past 3 years; a malignancy or history of malignancy (except for treated basal or squamous cell skin carcinoma or early forms of cervical carcinoma with no recurrence in 5 years); open wounds remaining after surgical treatment; prior treatment with apremilast; or a contraindication for apremilast.

Screening

Once a patient was considered eligible for the study, the following screening procedures were performed: (1) medical history and physical examination; (2) chest radiograph; (3) serologic testing for HIV, hepatitis B and C virus, tuberculosis (QuantiFERON) and (in women) a serum pregnancy test; and (4) clinical laboratory analysis to determine haemoglobin level, white blood cell count, absolute neutrophil count, platelet count, serum creatinine level, alanine aminotransferase level, and alkaline phosphatase level.

Study design

This study was an investigator-initiated clinical trial (EudraCT 2016-000859-27; NCT03238469) that was conducted in the department of Dermatology of the Erasmus University Medical Center Rotterdam, The Netherlands, approved by the local medical ethics committee (NL.57003.078.16), and implemented according to the Declaration of Helsinki principles. All patients provided written informed consent before enrolment. Eligible patients were randomly assigned to treatment with apremilast at a dose of 30 mg twice daily (n = 15) or placebo tablets with an appearance, packaging, and labelling identical to that of apremilast (n = 5). An independent statistician generated the randomisation scheme on the basis of the anticipated group size with a ratio of 3 to 1 by using R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria). Treatment was allocated by using the sequential randomisation code provided and guarded by the trial pharmacist. Patients, care providers, and

those assessing the outcomes were blinded to treatment allocation. Apremilast was dose-escalated over the first week of treatment (10 mg on day 1, with increases of 10 mg/d) until the target dose of 30 mg twice daily had been reached. The duration of the treatment period was 16 weeks. Study visits were scheduled for screening and at week 0 (baseline), week 2, week 4 (early response), week 8, week 12, and week 16 (end of study).

Outcome measures

The primary outcome was the percentage of patients reaching the Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16, which was defined as at least a 50% reduction in total abscess and inflammatory nodule (AN) count, with no increase in abscess count and no increase in draining sinus count relative to baseline.[15,16] At every visit, a physical examination (including a lesion count) was performed. Secondary clinical outcomes included the HiSCR at week 4, total lesion count, AN count, and Dermatology Life Quality Index (DLQI) score[17]; the patient's assessment of pain, itch, and disease burden on a numeric rating scale (NRS) ranging from 0 (no itch, pain, or burden) to 10 (unbearable/extreme itch, pain, and/or burden); and clinical photographs. Both physician-reported outcomes and patient-reported outcomes were collected at all visits. Safety assessments were conducted from screening until the end of the study. Adverse events (AEs) and vital signs were evaluated at each visit, and clinical laboratory measurements were evaluated at weeks 2, 8, and 16.

Statistical analyses

No statistical sample size was calculated.[18] Sample size estimations were based on previous exploratory clinical trials in HS.[19,20] Clinical efficacy and safety outcomes were analysed in the intention-to-treat population according to the randomised group assignments. The proportion of patients achieving HiSCR was analysed by Fisher's exact test at week 4 and week 16 (primary outcome). Missing outcomes in terms of the HiSCR of 2 patients at week 16 were imputed by last observation carried forward. To assess response over 16 weeks of treatment, the total lesion count, AN count, and DLQI score, as well as the patient's global assessment on pain, itch, and disease burden, were analysed by linear mixed effects modelling using analysis of covariance with the fixed factor treatment*time, the baseline value as covariate, and first-order autoregressive as best fitting covariance structure. Exactly the same model was subsequently used to separately evaluate the treatment arms relative to baseline for an impression of the short-term (week 4) and final response to treatment (end of the study [week 16]). Secondary outcomes were not statistically compared at time points to increase the power. Missing data for the analysis of covariance modelling were not imputed, nor were they carried forward. Post hoc analysis did not show

significant differences between the approach of no data imputation and the approach of last observation carried forward. Safety data were analysed by descriptive statistics for all patients who received at least 1 dose of the study drug. Statistical analyses were conducted with SPSS Statistics 24.0 (IBM Corporation, Armonk, NY). A 2-sided *p*-value less than 0.05 was considered significant.

RESULTS

Patients

Enrolment occurred between February and August 2017, and a 16-week follow-up was completed in December 2017. In total, 21 patients were randomised, of whom 20 received at least 1 dose of study medication and were included in the intention-to-treat population. Of these, 18 (90%) completed the week 16 follow-up visit (Figure 1). Of the 15 patients receiving apremilast, 2 (13%) discontinued the study: 1 patient discontinued between week 4 and week 8 because of personal circumstances (travel distance in combination with divorced parents), and the other discontinued at week 8 on account of adverse effects. None of the 5 patients in the placebo arm dropped out. The baseline characteristics for the intervention groups are depicted in Table 1.

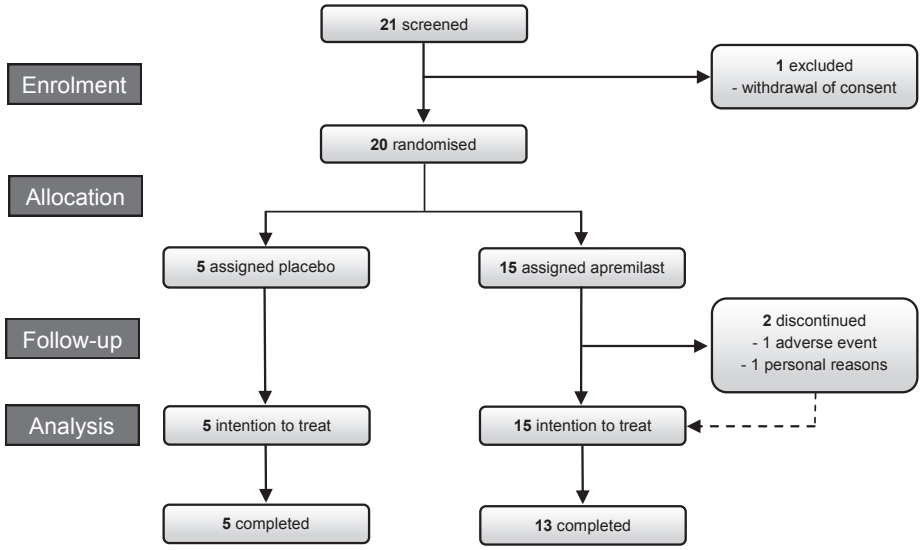

Figure 1. Flow chart of patient enrolment and the study procedure.

Table 1. Baseline characteristics.

Characteristic	Apremilast (n = 15)	Placebo (n = 5)
Mean age ± SD, y	35.7 ± 13.0	33.4 ± 8.2
Women, n (%)	12 (80)	5 (100)
Race, white, n (%)	15 (100)	4 (80)
Mean history of HS ± SD, y	21.6 ± 13.0	16.0 ± 7.1
Prior HS antibiotics treatment, n (%)	13 (87)	4 (80)
Prior HS biologics treatment, n (%)	4 (27)	2 (40)
Mean BMI ± SD, kg/m^2	32.7 ± 6.7	32.8 ± 5.3
Current smokers, n (%)	11 (73)	5 (100)
Mean current daily cigarette consumption ± SD	17.7 ± 8.2	19.6 ± 11.4
Mean total lesion count ± SD †	6.9 ± 2.3	7.2 ± 2.6
Mean AN count ± SD ‡	6.1 ± 1.7	5.8 ± 2.4
Mean DLQI ± SD, (0-30)	14.6 ± 7.6	11.8 ± 5.9
Mean NRS for pain ± SD, (0-10)	6.4 ± 2.4	5.8 ± 2.2
Mean NRS for itch ± SD, (0-10)	5.0 ± 2.9	6.8 ± 3.0
Mean NRS for disease burden ± SD, (0-10)	6.2 ± 2.1	7.0 ± 3.0

Values as mean ± standard deviation or number (percentage). † Total number of abscesses, draining sinuses/tunnels, and inflammatory nodules. ‡ Total number of abscesses and inflammatory nodules. AN: abscess and inflammatory nodule. BMI: body mass index. DLQI: Dermatology Life Quality Index. HS: hidradenitis suppurativa. NRS: numeric rating scale. SD: standard deviation.

Primary efficacy outcome

Of the 15 patients allocated to treatment with apremilast, 8 (53.3%) achieved a positive HiSCR at week 16 compared with none of the patients in the placebo group (p = 0.055) (Figure 2). The last observation was carried forward for the dropout after week 4 (negative HiSCR) and the dropout at week 8 (positive HiSCR). At week 4, 10 of 15 patients receiving apremilast (66.7%) achieved a positive HiSCR versus none of the patients in the placebo group (p = 0.033). A decrease in the proportion of patients treated with apremilast who achieved an HiSCR was observed from week 2 (an HiSCR in 11 of 15 patients) with a stabilisation between week 12 and 16 (a HiSCR in 8 of 15 patients). A characteristic example of the clinical response of a patient treated with apremilast is provided in Figure 3.

Secondary efficacy outcomes

Over 16 weeks of treatment, the patients receiving apremilast showed a significantly lower AN count (mean difference, –2.6; 95% confidence interval, –6.0 to –0.9; p = 0.011) (Figure 4) and significantly lower NRS scores for pain (mean difference, –2.7; 95% confidence interval, –4.5 to –0.9; p = 0.009) (Figure 5), itch (mean difference, –2.8; 95% confidence interval, –5.0 to –0.6; p = 0.015), and disease burden (mean difference,

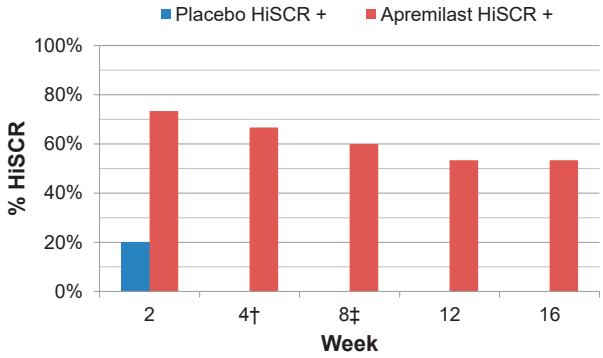

Figure 2. Percentage of patients in both treatment groups reaching the hidradenitis suppurativa clinical response (HiSCR) relative to baseline during the treatment period. Fisher's exact test was performed at week 4 (p = 0.033) and at week 16 (p = 0.055). † Last observation carried forward for 1 HiSCR non-achiever as a result of dropping out. ‡ Last observation carried forward for 1 HiSCR achiever as a result of dropping out.

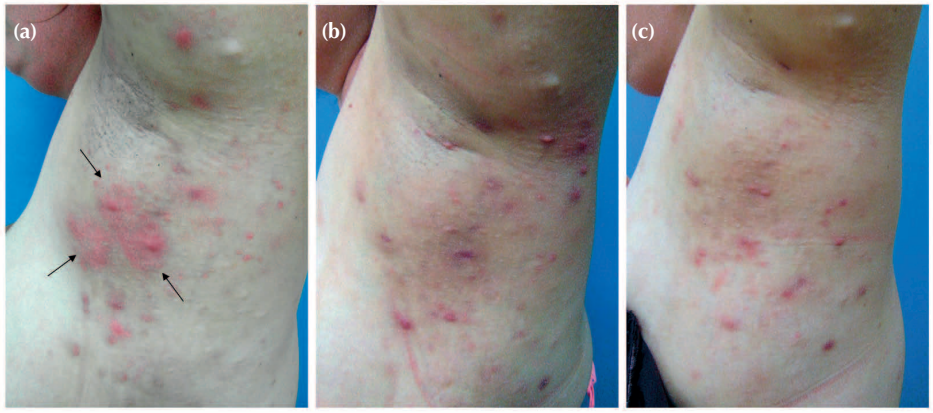

Figure 3. Example of a patient in the apremilast treatment group: baseline **(a)**, at week 4 (early response) **(b)**, and at week 16 (end of study) **(c)**. Arrows indicate index lesions (i.e. inflammatory nodules that were larger than 10 mm in diameter and painful by palpation at baseline. Note that all the deep-seated lesions have resolved. Erythematous lesions seen at week 16 are scars and superficial folliculitis.

−1.8; 95% confidence interval, −3.7 to −0.01; p = 0.049) than did patients in the placebo group. The total lesion count demonstrated a trend toward significant improvement in the apremilast group (mean difference, −2.6; 95% confidence interval, −5.5 to 0.2; p = 0.064). There were no differences in DLQI score over time between the treatment groups (mean difference, −3.4; 95% confidence interval, −9.0 to 2.3; p = 0.230).

The mean changes from baseline by treatment group for the secondary clinical outcomes at week 4 (early response) and week 16 (end of study) are summarised in Table 2. In the apremilast group the treatment outcomes observed at week 16 did

not further improve as compared with those at week 4 except for itch. In the placebo group all outcomes except the NRS for disease burden deteriorated at the end of study relative to week 4.

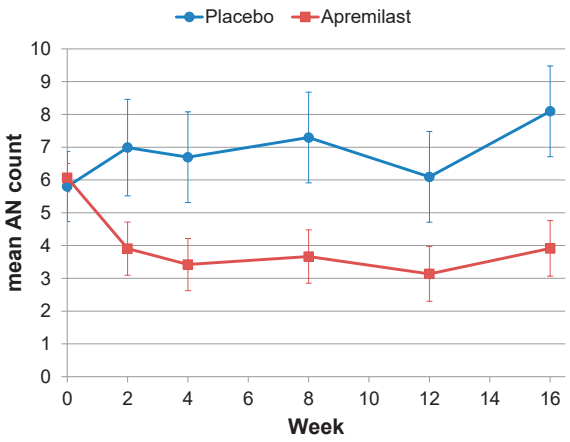

Figure 4. Mean estimated abscess and inflammatory nodule (AN) count from baseline until week 16 according to linear mixed effects modelling (analysis of covariance). Mean estimated difference for apremilast vs placebo: –2.6; 95% confidence interval, –6.0 to –0.9; $p = 0.011$. Bars display standard errors of the mean. AN count: total number of abscesses and inflammatory nodules.

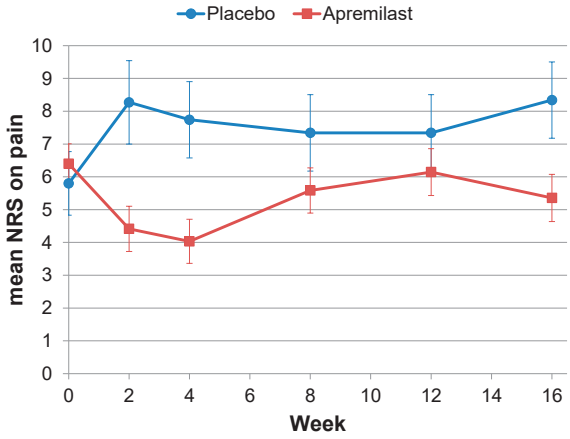

Figure 5. Mean estimated level of pain from baseline until week 16 according to linear mixed effects modelling (analysis of covariance). Mean estimated difference for apremilast vs placebo: –2.7; 95% confidence interval, –4.5 to –0.9; $p = 0.009$. Bars display standard errors of the mean. NRS: numeric rating scale.

Table 2. Mean estimated change from baseline for treatment outcomes at week 4 and week 16.

Characteristic	Apremilast* (n = 15)	Placebo* (n = 5)
Week 4		
Total lesion count†	−2.8 (−4.6 to −1.1)	−0.4 (−3.5 to 2.6)
AN count‡	−2.7 (−4.3 to −1.1)	+0.6 (−2.2 to 3.4)
DLQI (0-30)	−3.8 (−7.2 to −0.4)	+0.8 (−5.1 to 6.7)
NRS for pain (0-10)	−2.1 (−3.5 to −0.8)	+1.6 (−0.7 to 3.9)
NRS for itch (0-10)	−0.7 (−2.0 to 0.6)	+2.0 (−0.3 to 4.3)
NRS for disease burden (0-10)	−1.8 (−3.0, −0.6)	+1.1 (−1.0 to 3.2)
Week 16		
Total lesion count†	−2.0 (−3.9 to −0.2)	+1.4 (−1.7 to 4.4)
AN count‡	−2.2 (−3.9 to −0.5)	+2.0 (−0.8 to 4.8)
DLQI (0-30)	−2.3 (−5.9 to 1.3)	+4.2 (−1.7 to 10.1)
NRS for pain (0-10)	−0.8 (−2.2 to 0.6)	+2.2 (−0.1 to 4.5)
NRS for itch (0-10)	−1.1 (−2.5 to 0.3)	+2.4 (0.1 to 4.7)
NRS for disease burden (0-10)	−1.0 (−2.3 to 0.3)	+0.9 (−1.2 to 3.0)

* Mean estimated change from baseline at week 4 and week 16 for with corresponding 95% confidence intervals for outcome values according to linear mixed effects modelling (analysis of covariance). † Total number of abscesses, draining sinuses/tunnels, and inflammatory nodules. ‡ Total number of abscesses and inflammatory nodules. DLQI: Dermatology Life Quality Index. NRS: numeric rating scale.

Safety and tolerability

In total, 38 AEs were reported in the apremilast group versus 11 AEs in the placebo group (p = 0.514). An overview of the AEs is shown in Table 3. Most of the AEs were mild-to-moderate, and none was classified as a serious AE. One patient in the apremilast group discontinued study participation because of unbearable muscle and joint pain that occurred a few days after the first dose of study medication. A poststudy exploratory genetic analysis of cytochrome P450 family 3 subfamily A member 4 gene (*CYP3A4*) and cytochrome P450 family 1 subfamily A member 2 (*CYP1A2*) polymorphisms, which are important for the metabolism of apremilast, showed normal expression in this patient, implying that differential metabolism could not explain the AE. In all, 6 patients in the apremilast group versus 2 patients in the placebo group had ongoing AEs at the end of the study. The ongoing AEs in the patients receiving apremilast after 16 weeks were diarrhoea (n = 2), headache, nonspecific rash, increased fatigue, and a depressed feeling. At telephone follow-up 8 weeks after the end of study, these events were resolved without sequelae. There were no clinically significant changes in laboratory parameters.

Table 3. Adverse events.

Characteristic	Apremilast (n = 15) n (%) E*	Placebo (n = 5) n (%) E*
Headache	7 (47) 8	1 (20) 2
Diarrhoea	7 (47) 7	1 (20) 1
Nausea	4 (36) 4	1 (20) 1
Common cold	4 (36) 4	1 (20) 1
Vomiting	2 (13) 2	0 (0) 0
Nonspecific rash	2 (13) 2	0 (0) 0
Excessive joint and muscle pain	1 (7) 1^	0 (0) 0
Back pain	1 (7) 1	0 (0) 0
Increased fatigue	1 (7) 1	0 (0) 0
Depressed feeling	1 (7) 1	0 (0) 0
Pyelonephritis	1 (7) 1	0 (0) 0
Mycosis of the vulva	1 (7) 1	0 (0) 0
Increased itch	1 (7) 1	0 (0) 0
Sore throat	1 (7) 1	0 (0) 0
Elevation in serum ALT level†	1 (7) 1	0 (0) 0
Decrease in serum haemoglobin level‡	1 (7) 1	1 (20) 1
Nonspecific gastrointestinal symptoms	1 (7) 1	1 (20) 1
Dry mouth	0 (0) 0	1 (20) 1
Hair loss	0 (0) 0	1 (20) 1
Self-reported fever of unknown origin	0 (0) 0	1 (20) 1
Flare of herpes labialis	0 (0) 0	1 (20) 1

* Number of patients with at least one adverse event (n), percentage of patients with at least one adverse event (%), and number of adverse events (E). ALT: Alanine Transaminase. † Self-limiting elevation of 2-3 times the upper limit. ‡ Below lower limit according to local laboratory threshold. ^ Reason for dropout.

DISCUSSION

The main finding from this study was a clinically meaningful improvement of moderate HS after treatment with apremilast at a dose of 30 mg twice per day for 16 weeks. Apremilast significantly decreased disease activity as measured by the AN count, and 53.3% of patients receiving apremilast achieved the HiSCR in comparison with none of the patients receiving placebo. In addition, apremilast for 16 weeks was well tolerated by patients with moderate HS.

The response to treatment in this study was evaluated primarily by the HiSCR.[15] This validated efficacy end point has previously been used in 4 randomised controlled trials in HS.[5,16,21] The proportion of HiSCR responders in our study is within the range of HiSCR achievers in these previous studies: consecutively, 54.5% (adalimumab every week during 16 weeks of treatment [N = 147, of whom 43 received placebo]),

41.8% ([PIONEER I] adalimumab every week during 12 weeks of treatment (N = 307, of whom 154 received placebo]), 58.9% ([PIONEER II] adalimumab every week during 12 of weeks treatment [N = 326, of whom 163 received placebo]), and 60.0% (the monoclonal antibody MABp1 during 12 weeks of treatment [N = 20, of whom 10 received placebo]). Of note, in these trials patients with moderate-to-severe HS were enrolled and 3 of 4 studies were larger. Although a 1-to-1 comparison is inappropriate, the aforementioned results demonstrate that our findings are in line with the currently reported response rates.

Interestingly, the time to clinical response was much faster than that with apremilast in psoriasis, in which case an increasing proportion of patients achieving a 75% improvement in baseline Psoriasis Area Severity Index score has been observed up to 52 weeks after start of treatment.[22] This might potentially be explained by differences in underlying pharmacodynamic patterns, as HS auto-inflammatory pathology is initiated by an aberrant innate immune response followed by participation of the adaptive immune system that involves a broader array of cell types than in psoriasis pathophysiology.

Patients' assessment of HS-related pain and itch fluctuated during treatment, possibly reflecting the natural course of the disease, as the AN count does not take into account the size or severity of individual lesions. The DLQI score improved in the apremilast-treated patients but exhibited even larger variability during the study. An explanation might be the small number of patients studied and the fact that quality of life could have been affected by other (personal) circumstances in addition to the HS disease activity.

Treatment with apremilast at a dose of 30 mg twice daily was generally well tolerated, with the majority of the AEs rated mild-to-moderate. The safety profile of apremilast observed in this study is consistent with previous findings from larger trials in patients with psoriasis and psoriatic arthritis.[23,24] However, the number of patients included in our study was small, and the current safety results may not be representative for a larger population.

The evidence-based literature available on nonbiologic therapies in HS is limited and largely restricted to retrospective studies or expert opinion.[4] Therefore, recommendations for optimal medical management of HS are challenging. Although the efficacy of apremilast in HS must still be confirmed in larger studies, we believe that apremilast could be considered as a new treatment option for moderate HS after failure of conventional treatments, such as the combination of clindamycin and rifampicin. Currently, adalimumab is the first-choice agent in moderate-to-severe HS after failure of conventional treatments.[5] However, there may be advantages of apremilast over oral antibiotics and biologic therapies. It is well established that continuous antibiotic treatment can induce bacterial resistance, limiting its use for

chronic purposes, whereas subcutaneous administration and relatively frequent laboratory monitoring can pose an additional burden for patients who are treated with adalimumab. Another problem with the use of tumour necrosis factor-α antagonists such as adalimumab and infliximab is the risk of formation of antidrug antibodies, with neutralisation of the therapeutic effect over time.[25]

The major strength of this study is its randomised, double-blind, placebo-controlled design. In addition, the risk of inter-rater variability for the physician-reported outcomes was minimised by using only 2 clinical assessors. Limitations of our study are the small number of included patients, the study's relatively short duration, and the lack of data beyond the end of treatment. Missing HiSCR data were handled by using last observation carried forward in 2 patients taking apremilast, which potentially increased the effect of attrition bias. Furthermore, the AEs headache, diarrhoea, nausea, and vomiting were common in the apremilast group, which could have partially unblinded the observers.

In conclusion, the results from this study indicate that oral apremilast is a promising treatment option with good short-term safety and tolerability and that it could be a valuable addition to the armamentarium for the treatment of HS. Studies with larger populations and longer follow-up are needed to further elucidate the efficacy and safety profile of apremilast in HS.

REFERENCES

1 Jemec GB. Clinical practice. Hidradenitis suppurativa. *N Engl J Med* 2012; **366**: 158-64.

2 Vossen A, Schoenmakers A, van Straalen KR *et al*. Assessing Pruritus in Hidradenitis Suppurativa: A Cross-Sectional Study. *Am J Clin Dermatol* 2017; **18**: 687-95.

3 Kimball AB, Kerdel F, Adams D *et al*. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157**: 846-55.

4 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**: 619-44.

5 Kimball AB, Okun MM, Williams DA *et al*. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med* 2016; **375**: 422-34.

6 Theut Riis P, Thorlacius LR, Jemec GB. Investigational drugs in clinical trials for Hidradenitis Suppurativa. *Expert Opin Investig Drugs* 2018; **27**: 43-53.

7 Weber P, Seyed Jafari SM, Yawalkar N *et al*. Apremilast in the treatment of moderate to severe hidradenitis suppurativa: A case series of 9 patients. *J Am Acad Dermatol* 2017; **76**: 1189-91.

8 Papp K, Reich K, Leonardi CL *et al*. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol* 2015; **73**: 37-49.

9 Bissonnette R, Pariser DM, Wasel NR *et al*. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. *J Am Acad Dermatol* 2016; **75**: 99-105.

10 Edwards CJ, Blanco FJ, Crowley J *et al*. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis* 2016; **75**: 1065-73.

11 Schafer PH, Parton A, Gandhi AK *et al*. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol* 2010; **159**: 842-55.

12 Claveau D, Chen SL, O'Keefe S *et al*. Preferential inhibition of T helper 1, but not T helper 2, cytokines in vitro by L-826,141 [4-[2-(3,4-Bisdifluromethoxyphenyl)-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan- 2-yl)-phenyl]-ethyl]3-methylpyridine-1-oxide], a potent and selective phosphodiesterase 4 inhibitor. *J Pharmacol Exp Ther* 2004; **310**: 752-60.

13 Eigler A, Siegmund B, Emmerich U *et al*. Anti-inflammatory activities of cAMP-elevating agents: enhancement of IL-10 synthesis and concurrent suppression of TNF production. *J Leukoc Biol* 1998; **63**: 101-7.

14 Sbidian E, Chaimani A, Garcia-Doval I *et al*. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2017; **12**: CD011535.

15 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**: 1434-42.

16 Kimball AB, Sobell JM, Zouboulis CC *et al.* HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol* 2016; **30**: 989-94.

17 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210-6.

18 Bacchetti P, Deeks SG, McCune JM. Breaking free of sample size dogma to perform innovative translational research. *Sci Transl Med* 2011; **3**: 87ps24.

19 Miller I, Lynggaard CD, Lophaven S *et al.* A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. *Br J Dermatol* 2011; **165**: 391-8.

20 van der Zee HH, Laman JD, de Ruiter L *et al.* Adalimumab (antitumour necrosis factor-alpha) treatment of hidradenitis suppurativa ameliorates skin inflammation: an in situ and ex vivo study. *Br J Dermatol* 2012; **166**: 298-305.

21 Kanni T, Argyropoulou M, Spyridopoulos T *et al.* MABp1 Targeting IL-1alpha for Moderate to Severe Hidradenitis Suppurativa Not Eligible for Adalimumab: A Randomized Study. *J Invest Dermatol* 2018; **138**: 795-801.

22 Reich K, Gooderham M, Bewley A *et al.* Safety and efficacy of apremilast through 104 weeks in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: findings from the LIBERATE study. *J Eur Acad Dermatol Venereol* 2018; **32**: 397-402.

23 Papp K, Cather JC, Rosoph L *et al.* Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet* 2012; **380**: 738-46.

24 Schett G, Wollenhaupt J, Papp K *et al.* Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2012; **64**: 3156-67.

25 Vincent FB, Morand EF, Murphy K *et al.* Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis* 2013; **72**: 165-78.