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ORIGINAL PAPER

A randomized placebo-controlled single-center pilot study of the safety and efficacy of apremilast in subjects with moderate-to-severe alopecia areata

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Abstract

Alopecia areata (AA) is a common autoimmune disease that results in non-scarring hair loss. AA pathogenesis is thought to involve multiple inflammatory cytokines. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor that reduces pro-inflammatory cytokine production. Recent studies demonstrate upregulation of PDE4 in human scalp lesions of AA patients and hair regrowth in a humanized AA mouse model upon apremilast treatment, suggesting a possible potential of apremilast in AA. To assess the efficacy and safety of apremilast in AA, we conducted a double-blind, placebo-controlled single-center pilot study in 30 moderate-to-severe AA patients (≥ 50% scalp involvement) that were randomized 2:1 to receive apremilast ($n = 20$) or placebo ($n = 10$) orally for 24 weeks. The primary endpoint was the percentage of patients achieving 50% reduction in severity of alopecia tool (SALT) score ($SALT_{50}$) at 24 weeks compared to baseline, and the secondary endpoints included the percent change in SALT score at weeks 24 and 48. Eight patients in the apremilast arm withdrew prior to week 24 along with two patients in the placebo group, mostly due to lack of efficacy and adverse events. At 24 weeks, only 1 of 12 apremilast-treated subjects achieved $SALT_{50}$, and similarly 1 of 8 placebo-treated subjects achieved $SALT_{50}$. The difference between the mean percent improvement in SALT score at week 24 compared to baseline of the two study arms was not statistically significant ($p = 0.38$). The lack of treatment response in most of our patients argues against a pathogenic role for PDE4 specifically in moderate-to-severe AA, but targeting this pathway may still be of value in patients with mild AA as there is less of an inflammatory burden in this population. However, future larger studies may be needed to conclude apremilast's lack of efficacy in moderate-to-severe AA.

Keywords Alopecia areata · Apremilast · PDE4 inhibitor · Placebo-controlled trial · Moderate-to-severe AA

Abbreviations

AA	Alopecia areata
SALT	Severity of alopecia tool

Introduction

Alopecia areata (AA) is a common T-cell-mediated autoimmune disease of the hair follicle and is characterized by non-scarring hair loss [12, 13]. The estimated lifetime risk of AA is 1.7% among the general population [37]. Although AA usually presents as one or several bald circular patches on the scalp, it can sometimes progress to total scalp hair loss [alopecia totalis, (AT)] or total body hair loss [alopecia universalis, (AU)] [30]. Unlike patients with limited hair loss, patients with extensive disease rarely have spontaneous

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hair regrowth. Unfortunately, AA relapses are common and only about one-third of patients are able to maintain long-lasting remissions [31].

AA patients often suffer from a significantly reduced quality of life because AA triggers high levels of anxiety and depression [8]. Furthermore, a study showed that AA is most highly associated with atopy and particularly with atopic dermatitis (AD), as well as other autoimmune diseases such as thyroid disease, vitiligo, lupus erythematosis, and rheumatoid arthritis [17].

The pathogenesis of AA is still not fully elucidated. Historically, T_H1 was considered the main pathogenic pathway in AA, but recent studies suggest involvement of other axes, including T_H2, T_H9/IL-9, T_H17, IL-23, and PDE4 [3, 14, 35, 36]. The lack of mechanistic understanding has prevented therapeutic development. Thus, current AA therapies are limited, nonspecific, and unsatisfactory [30]. These treatments include topical therapies such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs) that have low efficacy, contact sensitizers such as diphenylcyclopropenone (DPCPs) that cause irritation and pain, intralesional steroids that cannot be used for large areas, and systemic treatments (i.e., cyclosporine and oral corticosteroids) that result in general immunosuppression [1, 2, 9, 11, 20, 27, 28]. Recently, Janus kinase (JAK) inhibitors started being tested for AA [31]. Several small clinical trials [22, 25] and case reports [6, 18] show preliminary efficacy of JAK inhibitors in AA. However, oral JAK inhibitors cannot elucidate the pathogenesis of AA since they target several cytokine pathways [30]. Furthermore, JAK inhibitors may be associated with long-term safety concerns [26]. Thus, there is a large unmet need for safe and more targeted treatments for moderate-to-severe AA patients.

Recently, studies have shown the expression of several PDE4s to be significantly increased in AA scalp lesions and significantly reduced after successful treatment with ustekinumab, an IL-12/IL-23p40 inhibitor [15, 35]. Moreover, a recent study in humanized AA mouse models showed hair retainment with apremilast treatment [19]. Therefore, we hypothesized that PDE4 inhibitor can potentially provide a therapeutic strategy for patients with AA. We thus performed a clinical trial with apremilast, an oral PDE4 antagonist that is FDA-approved for psoriasis, in 30 moderate-to-severe AA patients (defined as $>50\%$ scalp involvement) randomized 2:1 to placebo.

Methods

Study design and oversight

We conducted an Institutional Review Board (IRB)-approved phase 2, randomized, double-blind placebo-controlled clinical trial to evaluate the efficacy and safety of apremilast in 30 moderate-to-severe AA patients (clinicaltrials.gov, no. NCT02684123). To analyze efficacy, we used the Severity of Alopecia Tool (SALT). Enrollment and disposition of the patients are shown in Fig. 1. The first part of the study consisted of a 24-week period in which subjects were randomized 2:1 to receive either oral apremilast (30 mg) or placebo twice daily (BID) for a period of 24 weeks. Forty-four patients were initially screened for eligibility, and 30 qualified patients were randomized. Subjects from the apremilast group that achieved $SALT_{50}$ (percent of patients achieving a $\geq 50\%$ reduction in their SALT score compared to baseline) at week 24 and all subjects from the placebo group were eligible to enter phase II of the study. In this period, patients received apremilast (30 mg) BID up to week 48. In the apremilast group, 12 out of the 20 patients completed phase I. Of these, only one patient was eligible to continue into phase II, but she decided not to. In the placebo group, eight out of the ten patients completed phase I. Of these patients, only two continued to phase II, with only one patient reaching study completion at week 48.

Patients

Table 1 lists the demographic data of the 30 AA subjects in the study (21 females and 9 males; age range 20–72 years; mean age 41.8 years old). The mean age of the patients was 37.1 years in the treatment group and 44.15 years in the placebo group. The treatment group consisted of 16 females and 4 males, and the placebo group consisted of 5 females and 5 males. The baseline mean SALT score was 88.0 for the apremilast group and 87.7 for the placebo group. There were no significant differences in the demographics and clinical characteristics between the placebo and apremilast arms of the study, except for AA duration ($p=0.05$). In the total cohort of subjects, AA duration ranged from 1 to 10 years, with a mean AA duration of 5 years. While patients in apremilast had a little bit less duration of disease and the p value between the apremilast and placebo groups was significant, both groups had AA disease duration of less than 10 years. The main inclusion criteria for the study included patients ≥ 18 years of age, AA scalp involvement of $\geq 50\%$, and AA duration of more than 6 months and less than 10 years. Detailed inclusion and exclusion criteria are provided in Supplementary Table 1. All patients gave written informed consent before inclusion in the study.

Efficacy measures

The primary endpoint for the study was the proportion of patients achieving $SALT_{50}$ or greater at 24 weeks compared to baseline. The secondary endpoints of the study included percent change in SALT score at weeks 24 and 48 (see

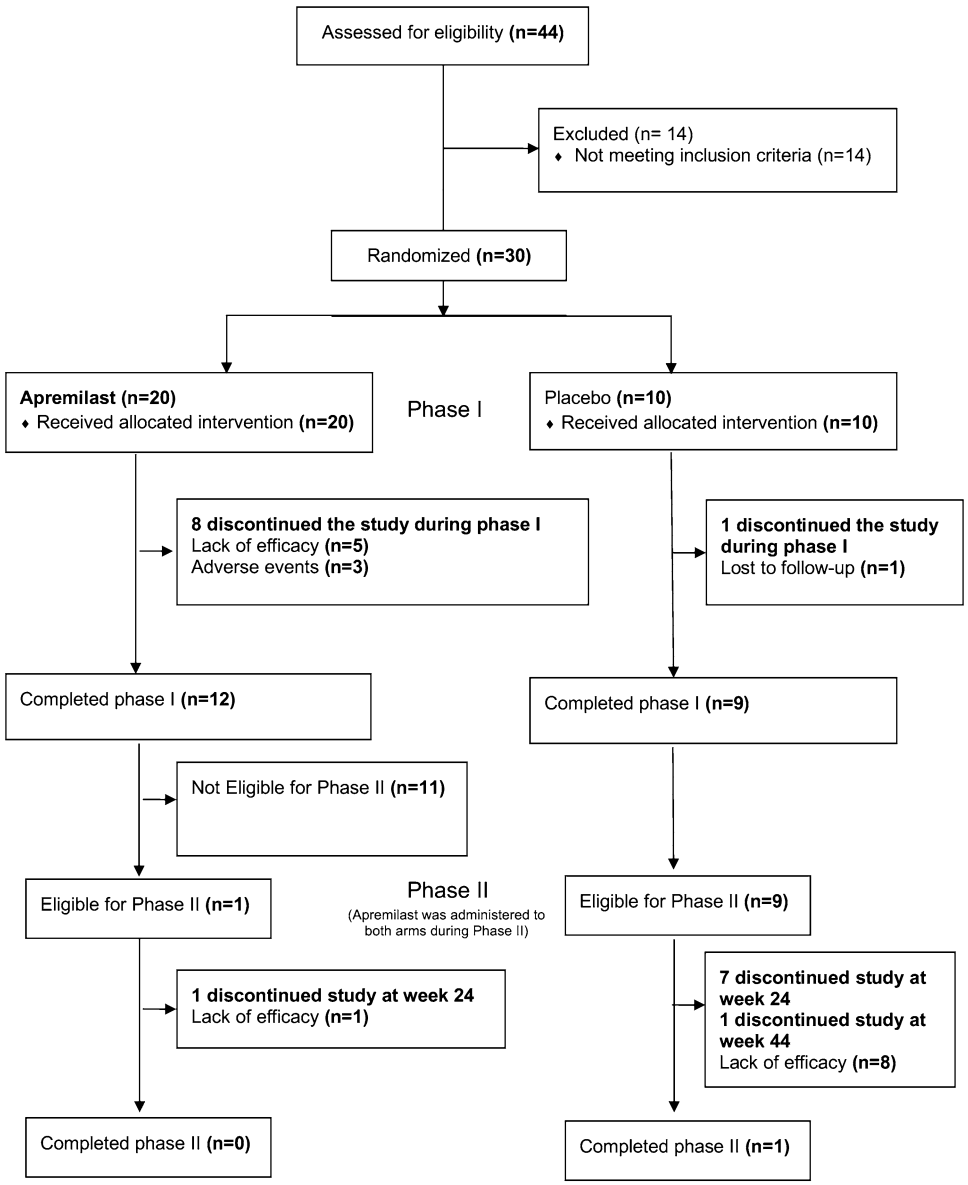

Fig. 1 Patient disposition

Supplementary Table 2). In both phases, adverse events and concomitant medications were assessed at each visit, and periodic laboratory monitoring was performed. Eyebrows, eyelashes, or non-scalp hair was not evaluated.

Statistical analysis

The mean percent improvement in SALT score was calculated for each group up to week 24 and statistical significance was calculated between drug and placebo arms by conducting a two-sided unpaired Student's *t* test. The number of adverse events from the drug vs placebo groups was compared using the Wilcoxon test. In addition, the Fisher's exact test was used to make a comparison between drug and placebo groups, using the ratio of patients that had an adverse event over the total number of adverse events recorded. Statistical significance was set at a two-tailed P value < 0.05.

Results

Patients and efficacy

30 AA patients were randomized 2:1 to apremilast ($n = 20$) and placebo ($n = 10$). A total of 20 patients completed phase I of the study, with 12 in the apremilast arm and 9 in the placebo arm. Eight patients in the apremilast group discontinued treatment during phase I, with five withdrawing due to lack of efficacy, two withdrawing due to nausea (one of these patients also reported lack of efficacy as an additional reason), and another patient withdrawing due to

Table 1 Demographics and clinical characteristics at baseline (N = 30)

Variable	Apremilast (*N* = 20) (%)	Placebo (*N* = 10) (%)	*P* value
Age (years) (mean ± SD)	37.1 ± 14.4	44.15 ± 16.9	0.25
Sex			
Female	16 (80)	5 (50)	0.20
Male	4 (20)	5 (50)	
Ethnicity			
Hispanic or Latino	3 (15)	1 (10)	1.00
Not Hispanic or Latino	17 (85)	9 (90)	
Race			
Asian	1 (5)	0 (0)	0.74
Black or African American	1 (5)	1 (10)	
White	17 (85)	9 (90)	
Unknown/not reported	1 (5)	0 (0)	
Duration of AA (years) (mean ± SD)	4.3 ± 2.7	6.6 ± 2.8	0.05*
Baseline SALT score (mean ± SD)	88.0 ± 19.8	87.7 ± 16.1	0.97

AA alopecia areata, *SD* standard deviation

*$P < 0.05$

nausea, diffuse arthralgia, and diarrhea. One patient in the placebo arm discontinued due to loss of follow-up. Only one patient in the apremilast group and one patient in the placebo group reached the primary endpoint, with a SALT improvement of 52% and 57%, respectively, at week 24 compared to baseline. Of the other apremilast patients that reached week 24, one had a 3.2% improvement while another had 2.5% SALT improvement at week 24 compared to baseline. On the other hand, two patients in the apremilast group had clinical worsening of AA, as shown by a 32.6% and 7.8% increase in their SALT scores at week 24 compared to baseline. Seven patients in the apremilast arm had no change (0%) in their SALT score at week 24 compared to baseline. By week 24, two additional patients in the placebo arm had improvement of their SALT scores by 15.6% and 8.69%, one patient had a worsening of SALT by 0.93%, and five patients had no change (0%) from their SALT baseline score. The mean SALT scores at 24 weeks were higher in the apremilast arm (mean SALT = 91.48) than in the placebo arm (mean SALT = 82.91), but were not significantly different ($p = 1.00$) (Fig. 2, Supplementary Table 3). The mean percent improvement in SALT score at week 24 compared to baseline was higher in the placebo arm (mean percent improvement = 9.01%) compared to the apremilast group (mean percent improvement = 1.45%), although it was also not statistically significant ($p = 0.38$). Therefore, apremilast yielded no significant improvement in hair regrowth over placebo.

Only one of the patients in the apremilast group was eligible to enter phase II, but she decided not to continue due to lack of efficacy. In the placebo group, only two of the eight eligible subjects continued into phase II, with one patient discontinuing the study after week 40 and one patient completing the study at week 48. The patient that discontinued after week 40 had no change (0%) in SALT score improvement at week 40 compared to week 24 (when they began receiving apremilast). The patient that completed the study had an 87% improvement in SALT score at week 48 compared to week 24. Although there is a discrepancy between these two patients that started on placebo and transitioned to apremilast, larger studies are needed in the future to make any definitive conclusions.

Safety

Adverse events occurred with a similar frequency in the apremilast and placebo groups (Table 2). The most common adverse event was nausea, occurring in four of the patients receiving apremilast. There were no serious adverse events in the drug or placebo arms. A total of 13 and 7 adverse events were reported in the drug and placebo groups, respectively; the numbers of adverse events were not significantly different between arms. Weight loss was not reported in any of the subjects.

Discussion

Alopecia areata is an autoimmune disease that results in patchy, non-scarring hair loss due to $CD4^+$ and $CD8^+$ T-cell-mediated damage of hair follicles [7, 40]. Although there are some treatment options with limited efficacy available for AA, there is no cure and no universally proven therapy that induces and maintains AA remission [16]. AA has a

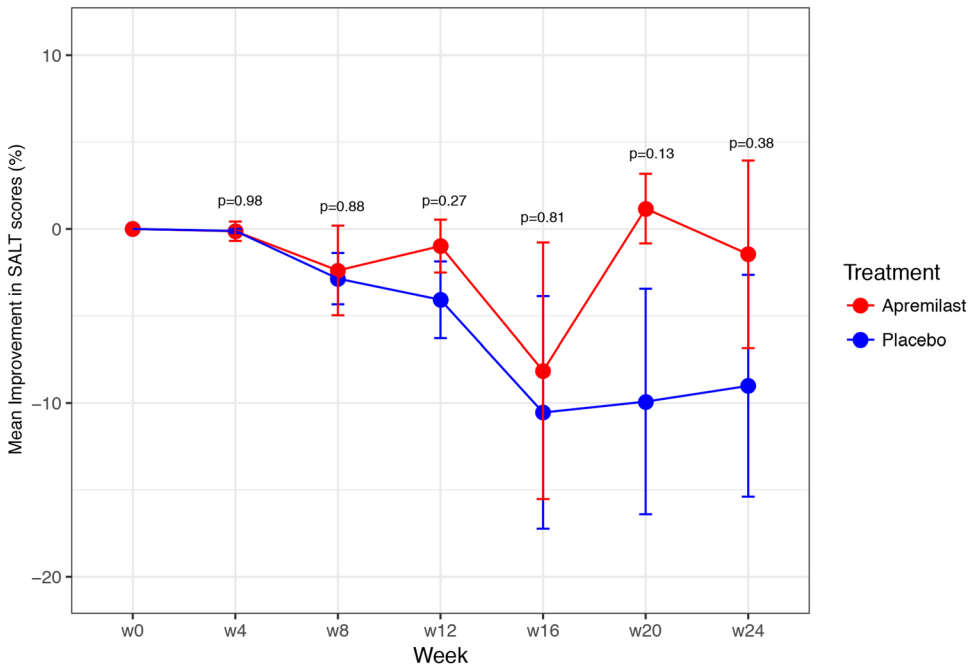

Fig. 2 Mean percent improvement in SALT scores from baseline to week 24

Table 2 Adverse events

	Apremilast ($N=20$)	Placebo ($N=10$)	p value
No. of adverse events	13	7	–
No. of patients with most common to least common side effects	–	–	–
Nausea	4	3	0.66
Diarrhea	3	1	1
Upper respiratory tract infection	1	1	1
Fatigue	0	1	0.33
Tinea pedis	1	0	1
Diffuse arthralgias	1	0	1
Headache	1	0	1
Migraine	1	0	1
Hypertension	1	0	1
Acute sinusitis	0	1	0.33
Mean no. of adverse events per patient	0.65	0.7	0.9
No. of patients with any adverse event (%)	9 (45)	5 (50)	1
No. of patients with serious adverse event (%)[a]	0	0	1
No. of patients discontinue because of adverse event (%)	3 (15)	0	0.53

[a]A serious adverse event was defined as an event that was fatal or life threatening, required prolonged hospitalization, caused persistent or substantial disability or incapacity, a congenital anomaly or birth defect, or an event that was considered by the investigator to be a medically important event*$P<0.05$

complex immune pathogenesis, characterized by the accumulation of T cells at the hair bulb, but the specific immune infiltrates and cytokines are still actively being explored [39]. Historically, T_H1 was considered the main pathway of pathogenesis in AA, but recent blood studies also suggest a possible role for T_H2 axis cytokines [3, 36]. Furthermore, cytokine profiling of lesional scalp from 27 AA patients showed strong activation of T_H1, T_H2, T_H9/IL-9, IL-23 cytokines, and PDE4 [35]. In addition to this, studies based on sera from patients with AA also suggest involvement of the T_H17 axis [14, 36]. Thus, as with psoriasis and atopic dermatitis, AA is following a similar course of discovery of specific cytokines and T cells involved, which will hopefully allow for the use of novel targeted therapeutics [31]. Apremilast, which is an oral, broad-acting, small molecule phosphodiesterase-4 (PDE4) inhibitor, recently received

attention as a potential treatment for AA therapy [10, 30]. PDE4 normally hydrolyzes cyclic adenosine monophosphate (cAMP). Apremilast results in accumulation of cAMP, thus reducing pro-inflammatory cytokines [30, 31]. Specifically, in model systems, apremilast inhibits production of inflammatory mediators such as tumor necrosis factor (TNF), interleukin 12 (IL-12), IL-2, interferon γ (IFN- γ), and IL-8, while promoting anti-inflammatory mediators such as IL-10 [32]. Apremilast shows no selectivity among the individual PDE4 isotypes (A, B, C, and D), but is shown to be more potent in decreasing PDE4 activity as compared to hydrolyzing enzymes from other PDE families [33].

Our study is the only double-blind randomized study investigating the efficacy of apremilast in patients with moderate-to-severe alopecia areata. In a recently published case series of only nine patients with similar AA involvement of either ≥ 50% scalp hair loss or alopecia universalis (AU), the patients were treated with 30 mg of apremilast BID for inconsistent time periods, ranging from 3 to 6 months [mean 4.2 months, standard deviation (SD) 1.2 months], without a placebo control, and the results revealed lack of efficacy [23]. On the other hand, in humanized AA mice, apremilast was shown to cause almost complete hair retainment, significant decreases in inflammatory cytokines (IFN-γ), and histologically normal terminal hair follicles [19]. In human AA lesions, PDE markers were significantly upregulated at baseline and significantly reduced after clinical improvement of AA with IL-23 inhibitor (ustekinumab) treatment [15]. However, the discrepancy between the negative results found in our study and the case series, and the positive results of the humanized mouse or human profiling studies may be that disease characterization through these studies does not necessarily imply a pathogenic role for PDE4 in AA [23].

In our study, at the primary endpoint of week 24, 12 subjects remained in the treatment group, and 8 subjects remained in the placebo arm. Only one patient in the treatment group achieved $SALT_{50}$. It should be noted that this patient had AA duration for 5 years prior to apremilast treatment and had one of the lowest baseline SALT score of all the patients in this study (baseline SALT score = 51.4). It is known that in patients with milder and shorter duration AA, spontaneous remission is more common. Thus, based on this patient's disease duration and low baseline SALT score, the patient may have spontaneously recovered regardless of the study drug [24]. However, it is possible that this patient's improvement in SALT score was due to the effect of apremilast, and thus to make a conclusive decision on the therapeutic effect of this drug in AA patients, future studies with a larger sample size are needed.

There may have been various other factors that could have contributed to the lack of efficacy seen in most of our AA patients treated with apremilast. There have been reports that other commonly used treatments for AA, such as DPCP therapy, require at least 2 years to show a successful treatment response. Thus, it may be possible that longer treatment time may have been needed for apremilast to cause improvement [5]. However, this is difficult to achieve because apremilast causes many side effects such as nausea, headache, and diarrhea, leading to discontinuation of therapy [21]. It is also possible that the dose of apremilast was not sufficient to cause hair regrowth in these patients, similar to the results of apremilast use in AD (clinicaltrials.gov, NCT02087943), but the side effects of the drug preclude from increasing the dosage or frequency in future studies.

Our gene expression analyses for T_H1 markers such as CXCL9, CXCL10, and IFN- γ did not show statistical difference in scalp tissues of apremilast vs placebo-treated patients. However, recent data from psoriasis studies with patients treated with apremilast show that apremilast primarily targets the T_H17 axis, more than the T_H1 axis [29], perhaps explaining the lack of satisfactory response that we observed.

Since this was an exploratory study, it is important to keep in mind some of the limitations of the study. The sample size was kept relatively low and there was no formal power calculation in this study, thus making it difficult to develop generalizable conclusions.

Nevertheless, since apremilast was found to be inefficacious in most of our treated subjects, this suggests that a different treatment approach should be explored for the treatment of moderate-to-severe AA. These alternate treatments include more broad agents including JAK inhibitors, or more specific cytokine antagonists such as those that target T_H1, T_H2, and IL-23 pathways [30, 35]. Due to the preliminary studies showing different T-helper axes involved, studies have been conducted using JAK inhibitors, PDE4 inhibitors, T_H17/IL-23 inhibitors, and T_H2 antagonists in either mouse models or humans to help narrow down the immune mediators of AA [31].

While JAK inhibitors have shown consistent improvements in large case series in AA patients and small studies [4, 6, 18, 22, 34, 40], large placebo-controlled clinical trials are still needed to evaluate the safety and efficacy of JAK antagonists in extensive AA over extended periods [31]. Furthermore, since JAK inhibitors are broad acting and thus target cytokines common to several immune mediators including T_H1/IFN-γ, common γ_c cytokines (IL-2, IL-4, IL-7, IL-9, and IL-21), and IL-23, they cannot fully prove the pathogenesis of AA [31, 38]. To dissect which specific cytokines are involved in AA pathogenesis, it is necessary to conduct clinical trials with targeted therapeutics against the T_H1, T_H2, and IL-23 cytokines [35]. While our study yielded negative results, it provides important data as it shows that the PDE4 pathway is unlikely to have a pathogenic role in moderate-to-severe AA. However, targeting this pathway may still be of value in patients with mild AA as they have

less of an inflammatory burden [35]. However, future larger studies may be needed to support these conclusions.

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Compliance with ethical standards

Conflict of interest Daniela Mikhaylov, Ana Pavel, Christopher Yao, Giselle Singer, Mark Taliercio, Rachel Karalekas, John Nia, Peter Hashim, Grace Kimmel, Danielle Baum, Yasaman Mansouri, and Anjali S. Vekaria have no conflicts of interest to disclose. Dr. Emma Guttman-Yassky is a board member of Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae and Leo Pharma; has received consultancy fees from Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubishi Tanabe and Eli Lilly; and has received research support from Janssen, Regeneron, Celgene, BMS, Novartis, Merck, LEO Pharma and Dermira. Dr. Mark Lebwohl is an employee of Mount Sinai, which receives research funds from Amgen, Anacor Pharmaceuticals Inc, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Janssen Biotech, Kadmon Corporation, LEO Pharmaceuticals, MedImmune, Novartis Pharmaceuticals Corporation, Pfizer, Sun Pharmaceuticals Industries Ltd, and Valeant Pharmaceuticals. The authors did not receive any form of compensation, either directly or indirectly, from any company or agency related to the development, authorship, or publication of this article.

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