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A pilot study of the safety and efficacy of picolinic acid gel in the treatment of acne vulgaris

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Summary

Background Cost limitations, adverse effects or lack of efficacy limit the use of current topical therapies in mild to moderate acne vulgaris.

Objectives To determine the safety and efficacy of picolinic acid, a novel zinc finger therapy, in the treatment of mild to moderate acne vulgaris.

Methods Twenty subjects with mild to moderate acne vulgaris were treated at our centre during an open-label study with 10% picolinic acid gel (PCL-016) twice daily to the face over 12 weeks.

Results Fifteen patients completed the 12-week open-label study. A reduction of 58·2% ($P < 0·001$) in mean total lesion count, 55·5% ($P < 0·001$) in mean inflammatory lesion count and 59·7% ($P < 0·005$) in noninflammatory lesion count was seen in this population. No serious adverse events or clinically significant changes in laboratory values were noted.

Conclusions Results from this study suggest that 10% picolinic acid gel applied twice daily may be safe and effective in the treatment of mild to moderate acne vulgaris.

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Conflicts of interest

M.P.H. has been active in industry-sponsored research with picolinic acid. He has conducted reimbursed investigations for Novactyl, Inc. and has received travel grants from Novactyl, Inc. M.M.N. and M.J.A. have no financial conflicts of interest to declare.

Acne vulgaris is a widely prevalent condition that affects nearly 80% of the U.S. population aged 11–30 years, and most of the population at some point in their life.[1–3] Patients with this condition are most bothered by their appearance.[4,5] Affected patients are prone to embarrassment, social withdrawal, depression, anxiety, anger, scorn and stigmatization.[6–10] Higher unemployment rates have also been demonstrated in adults with acne vulgaris compared with those without acne.[11] Patients with acne vulgaris have similar levels of social, emotional and psychological impairments as patients with chronic illnesses such as asthma, arthritis and diabetes.[12]

The pilosebaceous unit is believed to be the primary site of pathology in acne vulgaris. The distribution of acne favours sites with the highest concentration of pilosebaceous units, such as the face, chest or back.[2,6,13,14] Four main processes have been suggested as factors in the development of acne vulgaris: sebaceous gland hyperplasia with increased sebum production, altered follicular growth and differentiation, follicular colonization with *Propionibacterium acnes*, and inflammation.[13,15–18] The primary lesion of acne vulgaris, the microcomedo, is formed as a result of sebaceous gland hyperplasia and alteration in follicular growth and differentiation. Resultant noninflammatory (open and closed comedones) or inflammatory (papule, pustule, nodule) lesions may later evolve. Scarring often results in severe cases, but may occur in instances of mild to moderate disease.[19,20]

Increasingly effective therapies have evolved in recent years as the pathogenesis of acne vulgaris has become better understood. Topical retinoids, antibiotics, benzoyl peroxide, azelaic acid and salicylic acid are currently the mainstays of treatment for mild to moderate acne vulgaris. Many patients fail to improve with these agents due to cost, adverse effects leading to noncompliance (i.e. irritation), or lack of therapeutic benefit. The use of oral antibiotics or systemic retinoids increases both the cost and the risks for adverse effects.

Picolinic acid is an intermediate metabolite of the amino acid tryptophan. It appears to play a key role in zinc transport. As a therapeutic agent, the molecule seems to work by perturbing zinc binding in zinc finger proteins (ZFPs). Picolinic acid has antiviral and antibacterial properties *in vitro* and *in vivo*, and also modifies the immune response alone and in conjunction with other cytokines. Picolinic acid was first evaluated in the treatment of herpes labialis.

Here we report the results in 20 subjects with mild to moderate acne vulgaris treated at our centre during an open-label, phase I study of 10% picolinic acid gel (PCL-016).

Patients and methods

Patients

Subjects were eligible for study participation if they were at least 18 years of age and had a clinical diagnosis of mild to

moderate acne vulgaris of the face at baseline. Subjects were required to have between 10 and 100 inflammatory lesions (papules and pustules) and no more than two nodules. Subjects were judged to be in generally good health as determined by the principal investigator. Subjects were excluded if they had other active skin diseases that may interfere with evaluation; had a beard or other facial hair that may interfere with evaluation; had a history of an allergic reaction or significant sensitivity to constituents of the study drug; had a poorly controlled medical condition; were female and pregnant or breastfeeding or considering becoming pregnant during the study; had a history of clinically significant drug or alcohol abuse in the last year; had participated in a clinical research study within 30 days of enrolment; or were considered unreliable or unable to understand protocol directions in the estimation of the investigator. Subjects with other forms of acne such as acne rosacea, acne excoriée, chloracne, acne conglobata, acne fulminans or drug-induced acne were excluded. Subjects with moderate to severe nodulocystic acne deemed by the investigator to require systemic treatment were also excluded.

All subjects provided written informed consent before inclusion into the study. The study protocol was approved by the Institutional Review Board of the Washington University School of Medicine.

Methods

All subjects received open-label 10% picolinic acid (PCL-016) gel (NV-02; Novactyl, Inc., St Louis, MO, U.S.A.) to be applied in a thin layer to affected areas of the face twice daily for 12 weeks. Picolinic acid was stored at room temperature at the study site. Subjects stored study medication at home at room temperature after it was dispensed to them.

Subjects were not permitted to use any treatments for acne vulgaris during the study. Subjects discontinued topical astringents for 1 day and other topical medications, such as antibiotics, antiseptics, corticosteroids and retinoids, for at least 2 weeks. Subjects discontinued systemic corticosteroids and oral antibiotics for at least 4 weeks. Systemic retinoids were discontinued for at least 6 months. All other systemic therapy for acne vulgaris required discontinuation for at least 3 months. Women using oral contraception were required to be taking the same contraceptive for at least 3 months prior to study entry and to agree to continue this therapy until after completion of the study.

Clinical and laboratory assessments were performed at weeks 0, 4, 8 and 12 after the start of therapy. Clinical assessments included physical examination and an acne lesion count. A Physician Global Improvement score was also determined at the final visit. Laboratory assessments included a full blood count, serum chemistry, urine pregnancy test (if applicable) and plasma picolinic acid level. Concomitant medications and drug compliance were reviewed at each visit. All adverse events were assessed and recorded including date and time of onset, description, severity, time course, duration, outcome and relationship to study drug. An additional visit was conducted at week 1 following the initiation of therapy for review of concomitant medications, adverse event query and laboratory assessments.

Photographs of subjects who gave written informed consent were taken at weeks 0, 4, 8 and 12. Photographs were taken with a Nikon N80 camera. Photographs were performed to document efficacy and were not used for statistical analysis.

The primary efficacy endpoints included improvement in the total inflammatory lesion count, total lesion count and global severity score at week 12 compared with baseline. Secondary efficacy endpoints included improvement in the total noninflammatory lesion count at week 12 compared with baseline. Safety variables evaluated included the incidence of adverse events, abnormalities in routing laboratory monitoring, and comparisons of pre- and post-treatment plasma picolinic acid levels. Efficacy and safety outcomes were designed to direct planning for larger, blinded phase II–III investigations.

Statistical analyses

P-values were obtained for both per protocol and intent-to-treat analyses using a paired t-test. Analyses performed using a single-sample t-test yielded identical values.

Results

Baseline characteristics

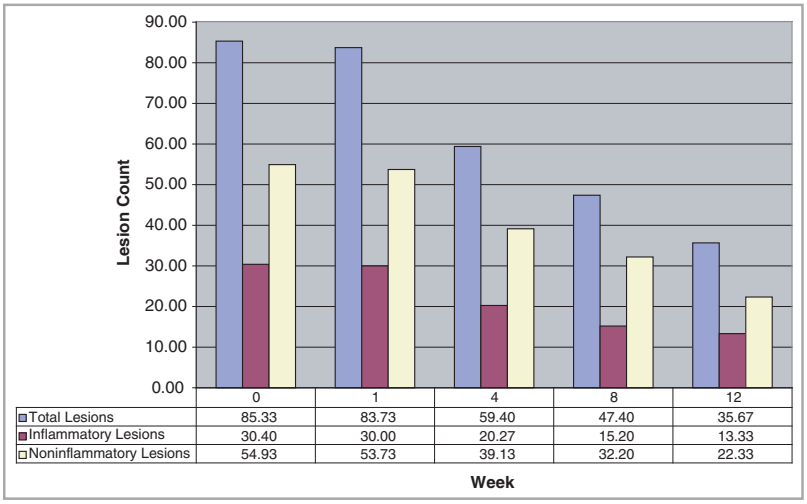
Twenty subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled in this study. Fifteen patients completed the 12-week open-label study per protocol. Four patients were lost to follow-up and one patient withdrew due to a localized adverse event (discussed later). Table 1 summarizes the baseline characteristics for the participants.

Efficacy

All 15 patients who completed the study demonstrated reduction in total lesion count and noninflammatory lesion count. Fourteen of these patients (93·3%) had a reduction in inflammatory lesion count. A reduction of 58·2% (from 85·33 to

Table 1 Baseline characteristics

Male	5
Female	15
Age range (years)	20–48 (mean 29·6)
White	12
African-American	6
Hispanic	1
Asian	1
Total baseline lesions	14–172 (mean 78·15)
Total baseline inflammatory lesions	12–58 (mean 27·45)
Total baseline noninflammatory lesions	2–148 (mean 50·7)



	0	1	4	8	12
Total Lesions	85.33	83.73	59.40	47.40	35.67
Inflammatory Lesions	30.40	30.00	20.27	15.20	13.33
Noninflammatory Lesions	54.93	53.73	39.13	32.20	22.33

Fig 1. Mean lesion counts using per protocol analysis.

35·67; P = 0·0001) in mean total lesion count, 55·5% (from 30·40 to 13·33; P = 0·0002) in mean inflammatory lesion count and 59·7% (from 54·93 to 22·33; P = 0·0007) in non-inflammatory lesion count was seen using per protocol analysis (Fig. 1).

Similar findings were demonstrated using intent-to-treat analysis for all 20 subjects enrolled into the study. A reduction of 50·6% (from 78·15 to 38·60; P = 0·0001) in mean total lesion count, 47·2% (from 27·45 to 14·30; P = 0·0001) in mean inflammatory lesion count and 52·4% (from 50·70 to 24·30; P = 0·0012) in mean noninflammatory count was seen using intent-to-treat analysis.

A Physician Global Improvement score was determined for each of the 15 patients completing the study at the final visit. Seven (47%) of these patients were judged to be almost clear (90–99% clearance) or to have marked improvement (75–89% clearance). Three patients (20%) had moderate (50–74% clearance) or minimal (25–49% clearance) improvement. Five patients (33%) were judged to have no change (0–24% clearance) from baseline.

Safety

Nineteen of the 20 patients enrolled were exposed to study drug for at least 1 week, 17 for at least 4 weeks, and 15 for all 12 weeks of the study. There were no deaths or serious adverse events noted during this study. There were no clinically significant changes in any laboratory values (full blood count and serum chemistry) during the study. No patients became pregnant during the study.

One of the 20 subjects enrolled (patient 2) experienced a drug-related adverse event leading to withdrawal from the study. This patient described 'burning' after application of study drug lasting 4 h that was 'too much'. This was classified by the investigator to be mild and probably related to study drug. There were no sequelae from this event. Two other patients described adverse events determined as probably related to study drug. Patient 15 noted burning after application lasting up to 1 h that resolved after the first week of therapy. Patient 6 described a sensation of 'facial tingling' on the first day of study drug application only. Table 2 summarizes each of the documented adverse events from this study.

Table 2 Adverse events

Patient	Adverse event	Week	Relation to study drug
2	Burning at application site	1	Probable
6	Tingling at application site	1	Probable
15	Burning at application site	1	Probable
12	Sinusitis	5	Possible
15	Allergic rhinitis	12	Possible
9	Vaginal yeast infection	8	Unlikely
11	Upper respiratory viral infection	9	Unlikely

Plasma measurements of picolinic acid were done using a validated assay developed by ABC Laboratories (now known as ABC Pharma Services, Columbia, MO, U.S.A.) for Novactyl, Inc. There were no stipulations regarding timing of blood draws relative to last dosing. Samples were collected in vacutainers containing powdered heparin. After gentle mixing, the samples were kept on wet ice and centrifuged within 15 min of collection. Resulting plasma was aliquoted and kept at −20 °C until analysis. Plasma levels of picolinic acid varied widely between patients and within patients during the study (Table 3). The maximum level detected was 113 ng mL^{-1}. No correlation between plasma picolinic acid levels and the occurrence of adverse events was evident.

Discussion

This study was designed to assess the clinical efficacy and safety of 10% picolinic acid gel, a novel immunomodulatory therapy targeting ZFPs, in the treatment of mild to moderate acne vulgaris. Results from this open-label study show picolinic acid

Table 3 Picolinic acid drug levels (ng mL^{-1})

Patient	Week 0	Week 1	Week 4	Week 8	Week 12
1	ND	13·6	17·6	11·3	BQL
2	BQL	BQL			
3	ND	17·9	54·5	BQL	47·0
4	BQL	52·3	90·5	BQL	BQL
5	ND	BQL	BQL	BQL	BQL
6	BQL	16·6	24·3	BQL	BQL
7	ND	72·6	113·0	44·9	BQL
8	BQL	BQL	BQL	BQL	BQL
9	BQL	15·5	BQL	BQL	BQL
10	BQL	96·0	91·2		
11	BQL	21·2	24·3	BQL	BQL
12	BQL	17·3	31·1	56·9	BQL
13	BQL				
14	BQL	BQL	BQL	BQL	BQL
15	BQL	BQL	BQL	BQL	BQL
16	BQL	31·9			
17	BQL	22·3	BQL	BQL	7·96
18	BQL	BQL	BQL	BQL	BQL
19	BQL	BQL	BQL		
20	BQL	39·8	57·4	BQL	29·3

ND, none detected on assay; BQL, below quantitative limit (< 10 ng mL^{-1}).

to be highly efficacious with 100% of the subjects who completed the study per protocol achieving a reduction in total and noninflammatory lesion count and 93·3% of subjects achieving a reduction in inflammatory lesion count. A clinically significant reduction in mean total lesion count, mean inflammatory lesion count and mean noninflammatory lesion count was seen using both intent-to-treat and per protocol analysis. In addition, nearly half of the patients (47%) who completed the study were almost clear or had marked improvement at the final visit using the Physician Global Improvement score.

Picolinic acid exists *in vivo* as a metabolite of the essential amino acid tryptophan. It is produced in approximately 25–50-mg quantities daily, assuming normal dietary intake. Picolinic acid chelates transition metal ions (i.e. Zn^{2+}) and is involved in the absorption and transport of transition metal ions.

Picolinic acid has been demonstrated to possess immunemodulating properties. Zinc binding within ZFPs is perturbed in the presence of picolinic acid. This leads to an alteration in chemokine expression independently and in the presence of other chemokines such as interferon-γ.[21,22] Picolinic acid has also been shown to have antiviral properties against herpes simplex virus type 1 and type 2. ZFPs are involved in viral replication, viral packaging and normal cell homeostatic functions. An Investigational New Drug application has recently been submitted by the manufacturer for picolinic acid cream in the treatment of herpes labialis.

A phase I cumulative irritant study was recently completed by Novactyl, Inc. assessing 10% picolinic acid cream in healthy volunteers. Patients applied 200-mg quantities daily under a patch for 21 consecutive days. The result of this irritant study was that 10% PCL-016 cream was clinically comparable with Blistex™ (Blistex Inc., Oak Brook, IL, U.S.A.).

There was only one adverse effect, burning at the application site, which led to patient discontinuation from this study. This was judged to be mild in intensity and probably related to study drug by the investigator. Another patient experienced burning after application of study drug that resolved within 1 week of the study. One patient described facial tingling present only on day 1 of study drug application. The remaining adverse effects discussed earlier were mild and judged as possibly related or unlikely to be related to study drug. There were no deaths or serious adverse events noted in this study. There were no significant laboratory abnormalities during the study.

It is estimated by the manufacturer that 10–20 mg of PCL-016 is delivered to the skin with each application of 10% picolinic acid gel. There was both intrapatient and interpatient variability in plasma levels of picolinic acid during the study. The maximum plasma level of picolinic acid detected was 113 ng mL^{-1}. No correlation between plasma picolinic acid levels and the occurrence of adverse events was evident. The minimum plasma picolinic acid level achievable before adverse effects are expected to occur, if a relation exists, remains to be elucidated.

In conclusion, the results of this study suggest that 10% picolinic acid gel applied twice daily may be safe and effective in the treatment of mild to moderate acne vulgaris. This is the first reported use of NV-02 in humans, and the first reported use of a zinc finger drug in the treatment of acne vulgaris. Future randomized, double-blind, multicentre trials will be necessary to confirm and better define these findings.

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