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Evaluation of Ixekizumab Treatment for Patients With Pityriasis Rubra Pilaris
A Single-Arm Trial

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IMPORTANCE Pityriasis rubra pilaris is a rare and disabling cutaneous disease that is frequently recalcitrant to conventional therapies and appears to involve interleukin (IL)-17 overexpression.

OBJECTIVE To investigate the clinical response and safety of ixekizumab in treating pityriasis rubra pilaris.

DESIGN, SETTING, AND PARTICIPANTS Single-arm, investigator-initiated trial conducted in adult patients with moderate to severe pityriasis rubra pilaris at a single-center academic university from June 2018 to January 2020. A total of 41 patients were screened, 12 were enrolled, and 11 completed the full duration of therapy. A referred, consecutive sample was used during participant selection. The treatment period and primary outcome occurred over 24 weeks with additional patient follow-up through 36 weeks.

INTERVENTION Subcutaneous administration of ixekizumab, a humanized IgG4 antibody that binds IL-17A, at the US Food and Drug Administration–approved dosing schedule for treatment of psoriasis for 24 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the mean change in Psoriasis Area and Severity Index at 24 weeks. Secondary outcomes included change in affected body surface area, quality of life, induction of sustained remission, and association of improvement with *CARD14* genetic variations and cutaneous cytokine expression.

RESULTS A total of 12 white patients (mean [SD] age, 49.8 [15.1] years; 8 male [67%]) were enrolled between June 2018 and April 2019, with 11 completing the full course of intervention. The mean (SEM) improvements in Psoriasis Area and Severity Index, affected body surface area, and Dermatology Life Quality Index were 15.2 (2.1) ($P < .0001$), 29.8% (9.3%) ($P = .009$), and 9.5 (2.5) ($P = .004$), respectively. The 4 participants with the most improvement in Psoriasis Area and Severity Index at week 24 stayed in remission at week 36 (defined as lack of increase in Psoriasis Area and Severity Index from week 24 through week 36), off therapy. Relative dermal IL-17A expression decreased by a 1.9 log-fold change. No participants had known pathogenic *CARD14* variations. There were no serious adverse events.

CONCLUSIONS AND RELEVANCE In this single-armed trial, ixekizumab was associated with reduced clinical signs and symptoms of pityriasis rubra pilaris in a subset of patients, including those in whom other systemic therapies have failed.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03485976

Supplemental content

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Pityriasis rubra pilaris (PRP) is a rare papulosquamous disorder with a clinically heterogeneous presentation. It is characterized by widespread follicular keratotic papules, diffuse erythema with classic islands of sparing, and palmoplantar keratoderma. PRP has been classified into 6 subsets, types I through VI, differentiated by age at onset, disease duration, and clinical features.[1-3] Familial cases of PRP have been associated with germline gain-of-function variations (formerly *mutations*) in the caspase recruitment domain family, member 14 (*CARD14*).[4] PRP symptoms have major effects on quality of life,[5] and more than half of patients diagnosed with PRP report comorbid depressive symptoms.[1]

To date, there have been no medications approved by the US Food and Drug Administration (FDA) for treatment of PRP. Off-label uses of cytotoxic agents and retinoids have been reported with varied results.[6] More recently, single case reports and small case series have shown promising outcomes with biologic agents for PRP,[7-12] including interleukin (IL)-17A antagonists[13-17] and IL-17 receptor antagonists.[18] To our knowledge, randomized clinical trials have not yet been performed in PRP, likely owing to the disease's rarity—the incidence of PRP has been estimated at 1 in 400 000 persons per year.[2]

IL-17A is the primary effector cytokine of type 17 helper (Th17) cells and has proinflammatory properties. IL-17A expression may be upregulated in patients with PRP, in addition to other cytokines in the Th17 axis.[19] Ixekizumab (Taltz, Eli Lilly and Company) is a humanized, monoclonal IgG4 antibody against IL-17A approved by the FDA in 2016 to treat adults with moderate to severe psoriasis.[20,21] We report the 24-week data of a single-arm interventional trial investigating ixekizumab for the treatment of PRP.

Key Points

Question Is ixekizumab an efficacious and safe treatment for moderate to severe pityriasis rubra pilaris?

Findings In this single-arm trial that included 12 adults, 7 achieved a 50% or greater reduction in clinical severity as measured by the Psoriasis Area and Severity Index, and there was a reduction in mean Dermatology Life Quality Index, itch, and pain scores. No serious or unexpected adverse events were observed.

Meaning Ixekizumab was associated with decreased clinical signs and symptoms of pityriasis rubra pilaris and no serious adverse events.

Methods

Trial Design

The primary aim of this single-arm, investigator-initiated trial was to determine the clinical response of patients with PRP to ixekizumab. Secondary aims included comparing quality of life related to PRP disease severity before and after ixekizumab treatment as well as exploring mechanisms by which ixekizumab is associated with alterations in the cutaneous inflammatory profile of PRP. A single-arm approach was chosen to provide sufficient power to evaluate treatment response in this rare patient population and provide preliminary data for therapeutic efficacy. This study received approval from the Oregon Health & Science University (OHSU) institutional review board (#18031) and was registered with ClinicalTrials.gov (identifier: NCT03485976). All participants gave written informed consent in accordance with the Declaration of Helsinki and received reimbursement for travel expenses in addition to compensation for each of the study visits. The trial protocol is provided in the Supplement.

Eligible patients were aged 18 to 99 years, had a diagnosis of PRP by clinical assessment from a qualified health care professional and a biopsy result consistent with PRP and not diagnostic for another disease, had moderate to severe disease (defined as Psoriasis Area and Severity Index [PASI][22] ≥ 10), and were candidates for systemic therapy and/or phototherapy. Clinical and pathology reports were obtained prior to the screening visit to establish diagnostic fidelity. Patients were excluded if they were previously treated with any therapeutic agent targeting IL-17, had any known malignant neoplasm or lymphoproliferative disease, or had any untreated chronic infections. Participants were required to discontinue all systemic therapies and/or phototherapy for PRP for 4 weeks or 5 half-lives prior to enrollment, whichever was longer, and remain off treatment for the duration of the study. Participants were permitted to continue any topical treatment(s) started prior to enrollment. Potential participants were identified through the OHSU electronic health record system, and publicity for the trial was established through the PRP Alliance, a patient advocacy organization, and ClinicalTrials.gov. Interested participants who contacted the study team were reached via telephone using institutional review board–approved recruitment material. Participants traveled to OHSU for the study from a widespread geographic area representing 10 states across the US.

Clinical photography, lesional and nonlesional tissue samples, and blood samples were obtained immediately prior to the first treatment dose and at the primary 24-week end point. Participants were treated with ixekizumab at the FDA-approved dosing schedule for psoriasis (160-mg subcutaneous injection at the first study visit followed by 80-mg subcutaneous injections every 2 weeks through week 12, then 80-mg subcutaneous injections every 4 weeks through week 20). Doses were administered by study staff or participants after in-person training during the first study visit, depending on participant preference. Clinician- and patient-reported outcome measures for nonprimary end point visits were obtained via secure videoconferencing for participants who lived more than 30 miles from OHSU. A follow-up visit was performed at week 36, 16 weeks after the final injection of ixekizumab, to assess for sustained remission. Clinician-reported outcomes included PASI, affected body surface area, 5-point static Physician Global Assessment (PGA) score, 5-point static Palmoplantar Physician Global Assessment (PPPGA) score, and Nail Psoriasis Severity Index (NAPSI).[23] Patient-reported outcomes included the Dermatology Life Quality Index (DLQI),[24] the 10-point itch numeric rating scale (NRS) score, as defined by the patient's usual itch over the last 7 days, and the 10-point pain NRS score, as defined by the patient's usual pain over

the last 7 days. A 4-point improvement in DLQI was considered clinically significant, as previously validated in inflammatory skin disease.[25] Safety assessments included clinical laboratory testing (performed at screening, week 4, and week 24), vital sign measurements (blood pressure and pulse taken at each visit), and complete physical examinations (performed at baseline and week 24). Additionally, participants were asked about adverse events at each visit. Given the open-label design, blinding of clinical- and patient-reported outcome measures was not performed. Sample size was estimated assuming a mean paired difference in PASI score before and after treatment of 8 points with an 8-point SD. Given these parameters, a minimum of 10 participants was required to detect a difference at the .05 level with a power of 80%. Because of the uncertainty inherent with this study, the goal number of participants to be recruited during the enrollment period was 15. All study procedures were conducted from June 2018 to January 2020.

Tissue Cytokine Levels

Skin punch biopsy samples were rinsed in sterile phosphate buffered saline without calcium or magnesium (HyClone Laboratories, GE Healthcare) and then incubated at room temperature in a 3.8% ammonium thiocyanate (Sigma Aldrich) in phosphate buffered saline without calcium or magnesium solution for 45 minutes. The epidermis and dermis were subsequently separated using sterile forceps, placed into separate RNase-free tubes containing 700 µL QIAzol (Qiagen), homogenized by hand using RNase-free pestles (Argos), and placed at −80 °C. All samples were collected, processed under sterile conditions, and stored within a 2-hour time frame. RNA was isolated using chloroform (Fisher Scientific), RNeasy Mini Kit (Qiagen), and RNase-free DNaseI (Qiagen). Briefly, 140 µL chloroform was added to each tube, the mixture was vortexed for 5 seconds, and the tubes were left to stand for 2 to 3 minutes at room temperature. After centrifugation at 12 000 g for 15 minutes at 4 °C, the top aqueous layer was transferred to a new tube and combined with an equal volume of 100% ethanol. Thereafter, the Qiagen RNeasy Mini Kit protocol was followed, ending with a 35 µL elution volume of RNase-free water. RNA quality was assessed on a Synergy H1 microplate reader (BioTek Instruments) with UV readings of 260 nm, 280 nm, 230 nm, and 320 nm. Purified RNA was stored at −80 °C until downstream analysis.

Total RNA was converted into total complementary DNA using High-Capacity RNA-to-cDNA Kit (ThermoFisher). Real-time quantitative reverse transcription-polymerase chain reaction was performed in triplicate using Power SYBR Green mix (ThermoFisher) on a QuantStudio 6 Real-Time PCR System (Applied Biosystems) with primers as follows: IL-17A (forward: CGATCCACCTCACCTTGGAA and reverse: TAGTCCACGTTCCCATCAGC), IL-23p19 (forward: GAGCCTTCTCTGCTCCCTGAT and reverse: CCTCAGGCTG CAGGAGTTG), IL-12p40 (forward: AGGGACATCATCAAACCTGACC and reverse: GCTGAGGTCTTGTCCGTGAA). The relative gene expression was calculated using the delta-delta-Ct method and normalized to GAPDH (forward: ATCAAGAAGGTGGTGAAGCA and reverse: GTCGCTGTTGAAGTCAGAGGA). Three data points were not available owing to low RNA yield from the dermis: 2 participants at baseline and 1 participant at the primary end point.

CARD14 Variation Analysis

Saliva was collected using a Saliva DNA collection, Preservation, and Isolation kit (Norgen Biotek Corporation). Preserved saliva samples were stored at room temperature until DNA isolation was performed. DNA was isolated from saliva according to the manufacturer's instructions. Primer sets representing all 20 exons of *CARD14*, including intron-exon boundaries, were generated with Primer3 (http://bioinfo.ut.ee/primer3-0.4.0/primer3/) using the hg18 version of the genome masked to exclude DNA sequence repeats (GenomeMasker, http://bioinfo.ebc.ee/snpmasker/) as the template. Polymerase chain reaction was conducted on 125 ng of DNA using KAPA2G Fast DNA Polymerase (Kapa Biosystems) and its products were sequenced. Resulting sequences were compared with the human reference sequence (hg18, NCBI) using Sequencher (Gene Codes Corporation).

Statistical Analysis

For the primary analysis, we used a 2-tailed, paired *t* test to compare mean improvement in PASI at week 24 with baseline. For secondary end points, comparisons of means were achieved with 2-tailed *t* tests at a significance level of $P < .05$. We performed analyses using the intention-to-treat complete case analysis principle. Analyses for the secondary and exploratory end points are described in the Supplement. Post-hoc analyses were completed to determine the percentages of patients achieving a 50%, 75%, or 90% reduction in PASI (PASI50, PASI75, and PASI90, respectively), and the association between clinical disease phenotype and treatment response. Post-hoc analysis of treatment response stratified by disease subtype was performed using a Fisher exact test. Normality was confirmed for all parametric statistics with the Shapiro-Wilk method. Statistical analyses were performed using Stata, version 15.1 (StataCorp LLC).

Results

Participants

A total of 12 white patients (mean [SD] age, 49.8 [15.1] years; 8 male [67%]) were enrolled between June 2018 and April 2019, with 11 completing the full course of intervention (**Figure 1**). One patient discontinued treatment after 7 days, citing lack of rescue therapy during the study period. The final week-24 primary end point visit was completed in October 2019, and the final week-36 visit was completed in January 2020. Baseline demographic and clinical characteristics are summarized in the **Table**. The mean (SD) baseline PASI score was 27.5 (12.3). Disease severity constituted a very large effect (DLQI, 11-20) or extreme effect (DLQI, 21-30) among 6 of 12 and 5 of 12 participants, respectively.[26] In addition, 11 of 12 patients (92%) were refractory to previous therapy; 3 of 12 (25%) participants had 1 previous systemic therapy fail, 2 of 12 (17%) had 2 previous systemic therapies fail, and 6 of 12 (50%) had 3 or more previous systemic therapies fail.

Figure 1. CONSORT Diagram

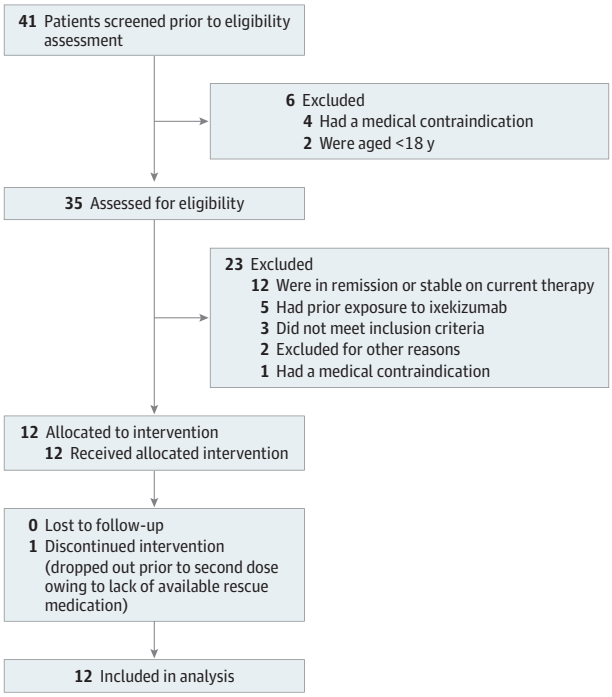


Table. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	No. (%) (N = 12)
Age, median (range), y	44.8 (23.2-73.2)
Male sex	8 (67)
White race	12 (100)
BMI,[a] median (range), kg/m^2	28.0 (19.4-44.6)
PRP subtype	
Classic adult (I)	6 (50)
Atypical adult (II)	5 (42)
Classic juvenile (III)	1 (8)
PASI, median (range)	24.8 (12.6-57.6)
Physician Global Assessment	
Clear (0)	0
Almost clear (1)	0
Mild (2)	0
Moderate (3)	9 (75)
Severe (4)	3 (25)
DLQI, median (range)	19 (9-28)
Itch NRS score, median (range)	7 (4-10)
Pain NRS score, median (range)	6 (3-9)
Age at diagnosis, median (range), y	43.7 (10.3-73.0)
Duration of symptoms prior to enrollment, median (range), mo	11.9 (1.4-453.8)
Previous systemic therapy	
Treatment naive	1 (8)
Prior systemic therapy	11 (92)
Prior methotrexate	6 (50)
Prior systemic retinoid	7 (58)
Prior biologic therapy	4 (33)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PRP, pityriasis rubra pilaris.

[a] Calculated as weight in kilograms divided by height in meters squared.

CARD14 results were available for 10 participants, none of whom had variations that appeared to be associated with PRP. Two participants had heterozygous single-nucleotide variants that were deemed unrelated owing to an allele frequency of 0.95% in the general population.

Clinical Outcomes

The mean (SEM) improvement in PASI from baseline to week 24 was 15.2 (2.1) ($P < .001$) on the 72-point scale (**Figure 2**). Seven of 12 patients (58%) achieved PASI50 from baseline at week 24 (Figure 2). Post-hoc analysis revealed the proportion of participants achieving PASI75 and PASI90 responses were 5 of 12 (42%) and 2 of 12 (17%), respectively. Additional post-hoc analysis did not suggest an association between clinical disease phenotype and treatment response; 3 of 6 participants (50%) with type I PRP, 3 of 5 (60%) with type II PRP, and 1 of 1 (100%) with type III PRP achieved PASI50 at week 24 ($P > .99$, Fisher exact test). Among those who achieved PASI50, PASI75, and PASI90, the mean (SEM) time to reach this degree of improvement was 6.9 (2.0) weeks, 12.8 (1.5), and 20.0 (4.0) weeks, respectively.

The mean (SEM) improvement in affected body surface area from baseline to week 24 was 29.8% (9.3%) ($P = .009$, Figure 2). The mean (SEM) improvement in the NAPSI from baseline to week 24 was not statistically significant: 9.7 (11.5) ($P = .42$) on the 160-point scale. Five of 12 participants (42%) achieved a PGA of clear (0) or almost clear (1) at the 24-week end point, and 4 of 12 participants (33%) achieved a PPPGA of clear (0) or almost clear (1) at week 24 (**Figure 3**).

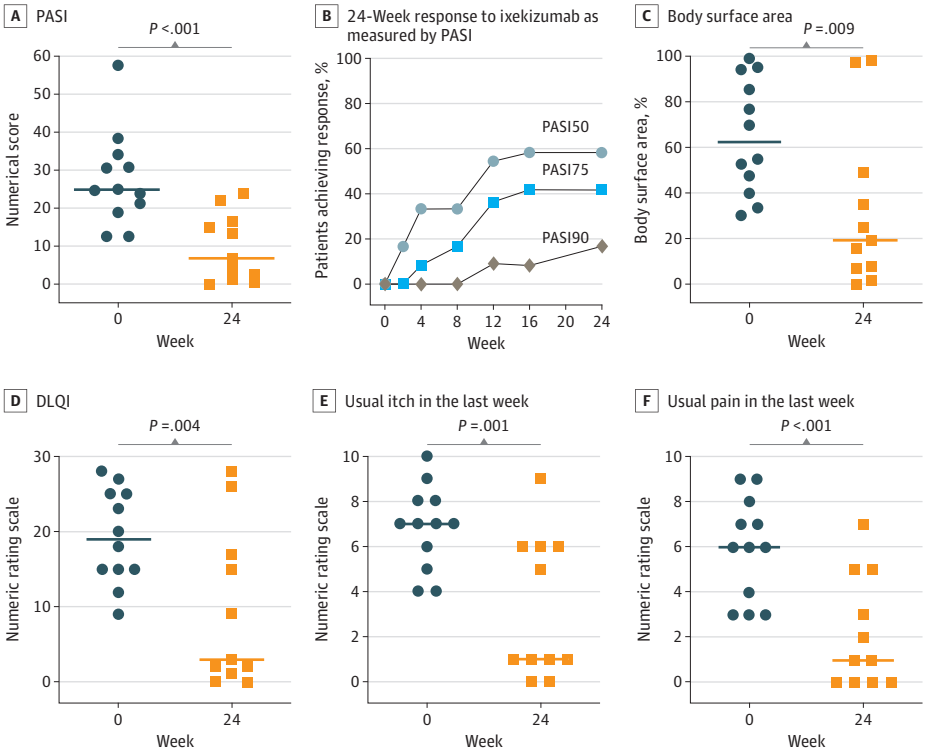
Nine of 12 participants (75%) achieved a 4-point improvement in the DLQI at week 24. Mean (SEM) improvement in DLQI over the 24-week period was 9.5 (2.5) points (Figure 2) out of a maximum 30 ($P = .004$). The mean (SEM) improvements in patient-reported itch NRS and pain NRS scores at week 24 were 3.6 (0.8) ($P = .001$) and 3.6 (0.7) ($P < .001$), respectively (Figure 2).

The 4 participants who had the most improvement in PASI score at week 24, ranging from 89% to 100% improvement, remained in remission off therapy at week 36. The 3 patients who had 52% to 84% improvement in PASI score during the treatment period had increases in PASI score after discontinuing ixekizumab. Two of these participants restarted an IL-17A inhibitor after the trial and subjectively reported clinical improvement. One participant who remained erythrodermic at the week-24 primary end point had a 7-point improvement in DLQI and 78% reduction in PASI at week 36. This participant reported to the study team that he chose to remain on ixekizumab at an increased dose of 80 mg administered subcutaneously every 2 weeks (independent of the study).

Safety

No serious or unexpected adverse events were observed over the study period. Minor adverse events occurred in 8 of 12 patients (67%), none of which interrupted the treatment protocol.

Figure 2. Clinician-Reported and Patient-Reported Outcome Measures at 24 Weeks



A, Mean Psoriasis Area and Severity Index (PASI) before and after therapy. Each point represents 1 participant. B, Aggregate response curves of the 12 participants. The overall score on the PASI ranges from 0 (clear skin) to 72 (worst possible disease). A PASI50 response indicates patients achieving a 50% or greater reduction from baseline. C, Mean affected body surface area before and after therapy. D, Mean Dermatology Life Quality Index (DLQI) on a 0-30–point scale before and after therapy. E, Mean usual itch and pain (F) over the last week measured by the patient on a 0-10–point numeric rating scale before and after therapy.

These events included upper respiratory tract infections (n = 4) and 1 occurrence of each of the following: gastrointestinal upset, injection site reaction, temporary PRP worsening, otitis externa, ingrown nail, glaucoma, nonspecific chest pain that resolved without intervention, mild leukopenia, eosinophilia, cutaneous atrophy attributed to topical corticosteroid use, and bacterial vaginosis.

Biomarker Assessment

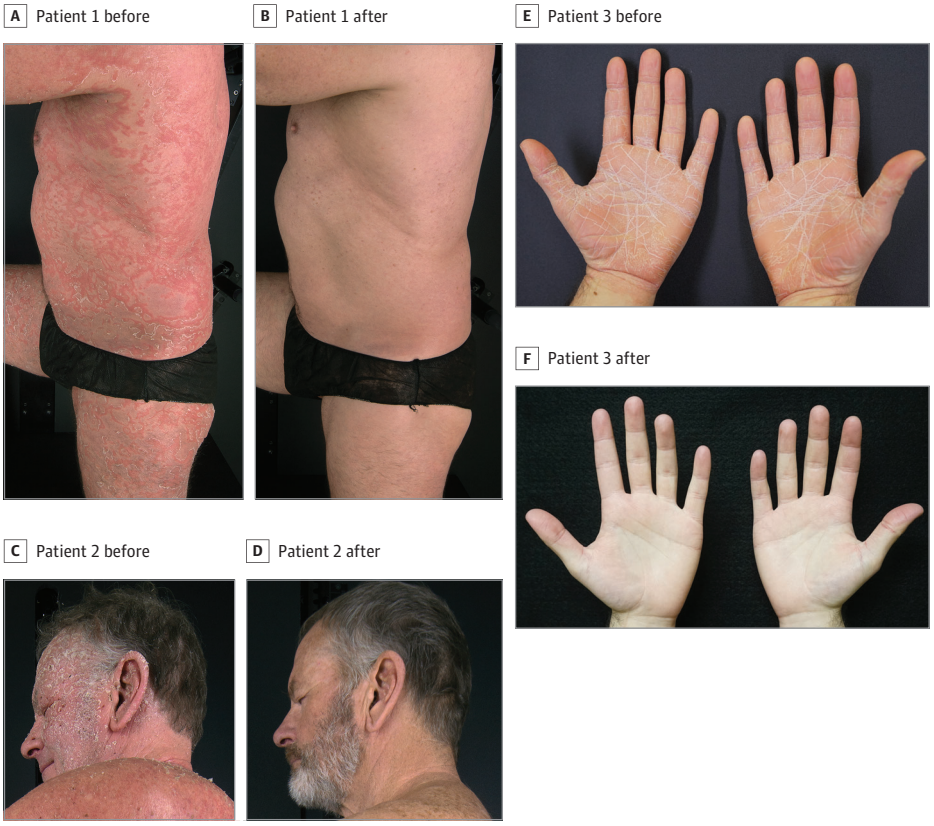
Assessment of pretreatment and posttreatment cytokine expression revealed a statistically significant overall reduction in relative dermal IL-17A expression by 1.9 log-fold change (P = .02) at week 24 compared with baseline (**Figure 4**). Reductions in epidermal IL-17A, IL-23p40, and IL-23p19 at week 24 compared with baseline were not statistically significant. When comparing participants with PASI50 response to nonresponders, differences in pretreatment or posttreatment epidermal and dermal IL-17A levels were not statistically significant.

Discussion

In this study, ixekizumab administered at the FDA-approved dosing regimen for psoriasis to patients with PRP for 24 weeks was associated with a mean improvement in PASI of 15.2, with 7 of 12 participants (58%) achieving a PASI50 after a mean of 6.9 weeks (Figure 2), and no serious or unexpected adverse events. We conclude that, consistent with previous case reports,[13,14,17] ixekizumab appears to be a safe and effective treatment for a subset of patients with PRP—including those with disease refractory to other therapies and those with type II PRP, which is conventionally treatment resistant.[15]

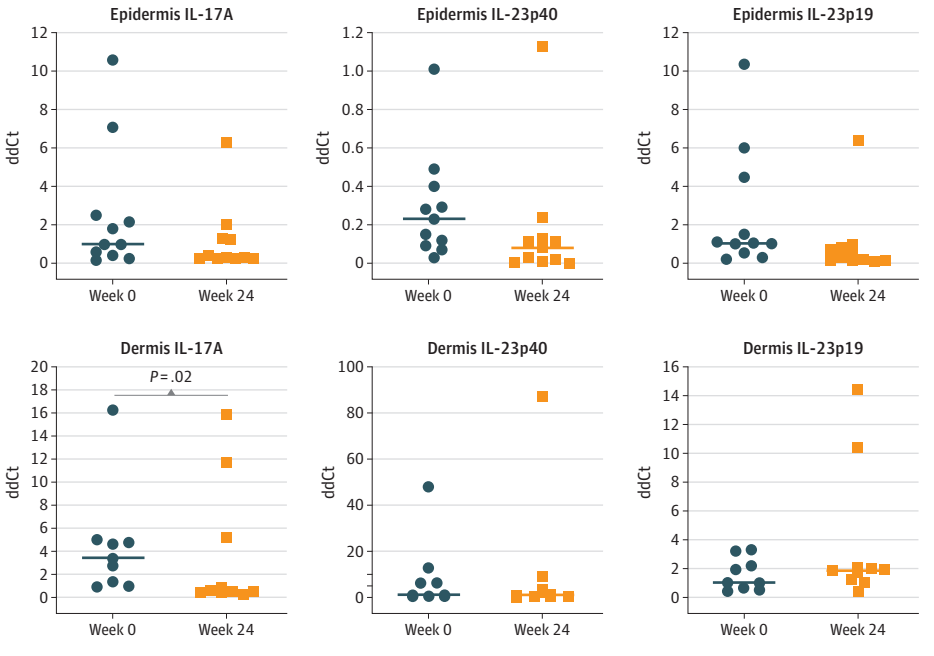
Participants in the present study had a considerable disease burden at the time of enrollment and markedly improved with therapy (Figure 3), as measured by both clinical signs and patient-reported symptoms (Table). A previous survey of PRP support group members given the Skindex-29 and DLQI surveys showed that PRP was associated with worse functional scores and among the worst symptom and emotional scores compared with other severe skin diseases.[5] Among the present cohort, 11 of 12 subjects rated their disease severity as having a very large effect (DLQI, 11-20) or an extreme effect (DLQI, 21-30) on quality of life at baseline.[26] Similarly, participants were noted to have an average PASI on enrollment of 27.5, more than twice the value at which plaque psoriasis is classified as severe disease.[27,28] Ixekizumab treatment was associated with considerable improvement in health-related quality-of-life scores as indicated by improvement in the DLQI survey, itch NRS, and pain NRS scores. Quality of life was increased by an average of 9.5 points on the DLQI survey, resulting in 6 of 12 participants (50%) achieving mild or no effect of their disease on quality of life. There were also clinically and statistically significant improvements in itch and pain NRS scores. Furthermore, treatment response was associated with improvement in quality of life. Given this condition's substantial disease burden, such associations should be considered in directing future prescribing patterns.

Figure 3. Clinical Photography Before Treatment and 24 Weeks After Treatment With Ixekizumab



Clinical photography demonstrating representative clinical response in 3 of 11 study participants who completed the trial. Each side-by-side photograph pair reflects a different participant to include representation from the entire cohort. The left photos were taken at trial enrollment and the right photos were taken at the week-24 primary end point.

Figure 4. Cutaneous Cytokines Before Treatment and 24 Weeks After Treatment With Ixekizumab



Fresh lesional skin biopsies were separated into epidermis and dermis. Relative mRNA levels were analyzed by quantitative real-time polymerase chain reaction in triplicate. Each dot on the graph represents the mean relative expression from 1 participant calculated by the delta-delta-Ct (ddCt) method. Week 0 (pretreatment) and week 24 (posttreatment) means were not significant except as indicated for dermis IL-17A.

Remission off therapy at week 36 was sustained in the 4 individuals who had the highest reduction in PASI at week 24. In these participants, sustained remission off therapy suggests that treatment was associated not only with decreased symptoms but also may have influenced the natural history of disease. Disease remission for all 4 patients was unlikely to be

spontaneous: 2 of the participants had atypical adult (type II) PRP that often does not spontaneously remit, and the other 2 with classic adult (type I) PRP had disease duration of less than 3 months when they started therapy. Previous reports of treatment with other biologic agents, such as ustekinumab[9,29] and etanercept,[11] have suggested similar findings to the present trial by inducing a complete and sustained remission after cessation of therapy. This finding may have significant implications in the cost-to-treat by shortening treatment duration.

It is also notable that all participants who completed the trial appeared to clinically improve after 24 weeks of ixekizumab therapy, even those who did not achieve PASI50. One participant who did not respond to the standard dose of ixekizumab at 24 weeks had improvement on a more frequent dosing schedule (increased from injection every 4 weeks to every 2 weeks), with a 65% PASI reduction at week 36 from the week-24 end point. We speculate that some patients with severe PRP may need higher doses of IL-17 blockade for optimal treatment response, although further studies for safety and efficacy are needed. Although largely unexplored, combination therapy may also be beneficial as suggested by a recent case report[17] of treatment effectiveness with a combination of an IL-17A inhibitor and acitretin. Response to ixekizumab did not appear to be associated with PRP subtype. There also did not appear to be any association between treatment response and extent of disease, phenotypic features, participant weight, or treatment history.

As expected, treatment with IL-17A inhibition was associated with a mean reduction in dermal expression of IL-17A, which supports results of previous case reports[19] and is similar to treatment of psoriasis.[30] PRP and psoriasis share overlapping clinical, genetic, and immunologic features but remain distinct diseases, especially in terms of the recalcitrance of PRP to conventional treatment. Future research aimed at global analysis of mRNA and protein levels in PRP skin lesions and serum will be valuable for identifying additional pathways of importance to PRP.

Germline heterozygous gain-of-function variations in *CARD14* have been associated with both PRP[4] and psoriasis.[31,32] More recently, the term *CARD14-associated papulosquamous eruption*, or CAPE, has been proposed to more accurately reflect the clinical and histopathologic features of this disease,[33,34] and *CARD14* gain-of function variations in mice were shown to activate IL-17 and IL-23 cutaneous inflammation.[35] None of the participants in our cohort had known pathogenic *CARD14* variations, so it remains uncertain if *CARD14*-associated disease would also respond to blockage of the IL-17 pathway.

Limitations

The present trial is not without limitations, including its small sample size; the nonrandomized, open-label design; and the racial and ethnic homogeneity of the participants. Other important limitations of this study are the lack of a criterion standard for diagnosing PRP and the lack of validated clinical outcome measures for this rare disease. Surrogate outcomes, such as the PASI and NAPSI, provide a reasonable estimation of effect size in psoriasis but do not capture certain features of PRP, such as the follicular nature, lichenification, and relatively nonadherent/shedding nature of the scale. The PGA has been validated in a number of cutaneous diseases, including psoriasis[36] and eczema,[37] and may represent disease response in a more interpretable manner. We also cannot rule out regression to the mean as an explanation of some of our results. Finally, with rare diseases such as PRP, referral bias cannot be avoided and particularly favors trial enrollment of patients in whom previous therapies had failed. The outcome of this referral bias would be an underestimation of the drug's association with response in the wider population given the higher proportion of patients with refractory disease enrolled in the trial.

Conclusions

Despite these limitations, the trial showed that ixekizumab is associated with decreased clinical signs and symptoms of PRP in a subset of patients, including those in whom previous other systemic therapies had failed. Larger, randomized, blinded, graded-dosing, and multicenter trials should further explore these results and additionally explore clinical and biochemical factors associated with treatment response.

ARTICLE INFORMATION

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Author Contributions: Dr Greiling had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Haynes, Topham, Greiling.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Haynes, Strunck, Topham, Greiling.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Haynes, Strunck, Greiling.
Obtained funding: Greiling.
Administrative, technical, or material support: Haynes, Strunck, Ortega-Loayza, Kent, Cassidy, Hu, Choate, Greiling.
Supervision: Greiling.

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REFERENCES

1. Ross NA, Chung HJ, Li Q, Andrews JP, Keller MS, Uitto J. Epidemiologic, clinicopathologic, diagnostic, and management challenges of pityriasis rubra pilaris: a case series of 100 patients. *JAMA Dermatol*. 2016;152(6):670-675. doi:10.1001/jamadermatol.2016.0091

2. Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol*. 1980;5(1):105-112. doi:10.1111/j.1365-2230.1980.tb01676.x

3. Miralles ES, Núñez M, De Las Heras ME, Pérez B, Moreno R, Ledo A. Pityriasis rubra pilaris and human immunodeficiency virus infection. *Br J Dermatol*. 1995;133(6):990-993. doi:10.1111/j.1365-2133.1995.tb06939.x

4. Fuchs-Telem D, Sarig O, van Steensel MA, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet*. 2012;91(1):163-170. doi:10.1016/j.ajhg.2012.05.010

5. Eastham AB, Tkachenko EY, Femia AN, et al. Pityriasis rubra pilaris: a study evaluating patient quality of life in 2 populations. *J Am Acad Dermatol*. 2019;81(2):638-640. doi:10.1016/j.jaad.2019.01.061

6. Kromer C, Sabat R, Celis D, Mössner R. Systemic therapies of pityriasis rubra pilaris: a systematic review. *J Dtsch Dermatol Ges*. 2019;17(3):243-259. doi:10.1111/ddg.13718

7. Maloney NJ, Hisaw LD, Worswick S. Refractory pityriasis rubra pilaris treated with etanercept, adalimumab, or ustekinumab: a retrospective investigation. *Dermatol Ther*. 2017;30(6). doi:10.1111/dth.12559

8. Aragón-Miguel R, Prieto-Barrios M, Calleja-Algarra A, et al. Refractory pityriasis rubra pilaris with good response after treatment with ustekinumab. *J Dtsch Dermatol Ges*. 2018;16(8):1022-1025. doi:10.1111/ddg.13550

9. Bonomo L, Raja A, Tan K, Guttman-Yassky E. Successful treatment of juvenile pityriasis rubra pilaris with ustekinumab in a 7-year-old girl. *JAAD Case Rep*. 2018;4(2):206-210. doi:10.1016/j.jdcr.2017.09.010

10. Ismail N, Callander J, Williams M, Anstey AV. Erythrodermic pityriasis rubra pilaris managed at home: intensive community care followed by ustekinumab. *Clin Exp Dermatol*. 2018;43(6):749-751. doi:10.1111/ced.13626

11. Lora V, De Felice C, Cota C, Graceffa D, Morrone A, Bonifati C. A case of juvenile pityriasis rubra pilaris type III successfully treated with etanercept. *Dermatol Ther*. 2018;31(1). doi:10.1111/dth.12577

12. Napolitano M, Lembo L, Fania L, Abeni D, Didona D, Didona B. Ustekinumab treatment of pityriasis rubra pilaris: A report of five cases. *J Dermatol*. 2018;45(2):202-206. doi:10.1111/1346-8138.14114

13. Hanfstingl K, Pekar-Lukacs A, Motz R, Guenova E, Hoetzenecker W. Successful treatment of pityriasis rubra pilaris with ixekizumab. *Case Rep Dermatol*. 2018;10(2):97-100. doi:10.1159/000488902

14. Heibel MD, Heibel HD. Successful treatment of type I pityriasis rubra pilaris with ixekizumab. *JAAD Case Rep*. 2018;4(8):774-776. doi:10.1016/j.jdcr.2018.05.006

15. Gauci ML, Jachiet M, Gottlieb J, et al. Successful treatment of type II pityriasis rubra pilaris with secukinumab. *JAAD Case Rep*. 2016;2(6):462-464. doi:10.1016/j.jdcr.2016.09.006

16. Schuster D, Pfister-Wartha A, Bruckner-Tuderman L, Schempp CM. Successful treatment of refractory pityriasis rubra pilaris with secukinumab. *JAMA Dermatol*. 2016;152(11):1278-1280. doi:10.1001/jamadermatol.2016.3885

17. Chastagner M, Hoelt P, Kanitakis J, Jullien D, Villani AP. Successful treatment of TNFα inhibitor-resistant pityriasis rubra pilaris with ixekizumab and acitretin. *Eur J Dermatol*. 2019;29(2):218-220.

18. De Rosa A, Gambardella A, Licata G, Alfano R, Argenziano G. Successful treatment of pityriasis rubra pilaris with brodalumab. *Australas J Dermatol*. 2019. doi:10.1111/ajd.13215

19. Feldmeyer L, Mylonas A, Demaria O, et al. Interleukin 23-helper T cell 17 axis as a treatment target for pityriasis rubra pilaris. *JAMA Dermatol*. 2017;153(4):304-308. doi:10.1001/jamadermatol.2016.5384

20. Griffiths CE, Reich K, Lebwohl M, et al; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551. doi:10.1016/S0140-6736(15)60125-8

21. Gordon KB, Blauvelt A, Papp KA, et al; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345-356. doi:10.1056/NEJMoa1512711

22. Fredriksson T, Pettersson U. Oral treatment of pustulosis palmo-plantaris with a new retinoid, Ro 10-9359. *Dermatologica*. 1979;158(1):60-64. doi:10.1159/000250744

23. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol*. 2003;49(2):206-212. doi:10.1067/S0190-9622(03)00910-1

24. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. doi:10.1111/j.1365-2230.1994.tb01167.x

25. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035. doi:10.1111/j.1365-2133.2008.08832.x

26. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125(4):659-664. doi:10.1111/j.0022-202X.2005.23621.x

27. Feldman SR. A quantitative definition of severe psoriasis for use in clinical trials. *J Dermatolog Treat*. 2004;15(1):27-29. doi:10.1080/09546630310019382

28. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology*. 2005;210(3):194-199. doi:10.1159/000083509

29. Ruiz Villaverde R, Sánchez Cano D. Successful treatment of type 1 pityriasis rubra pilaris with ustekinumab therapy. *Eur J Dermatol*. 2010;20(5):630-631.

30. Krueger JG, Fretzin S, Suárez-Fariñas M, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol*. 2012;130(1):145-54.e9. doi:10.1016/j.jaci.2012.04.024

31. Jordan CT, Cao L, Roberson ED, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet*. 2012;90(5):796-808. doi:10.1016/j.ajhg.2012.03.013

32. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet*. 2012;90(5):784-795. doi:10.1016/j.ajhg.2012.03.012

33. Craiglow BG, Boyden LM, Hu R, et al. CARD14-associated papulosquamous eruption: a spectrum including features of psoriasis and pityriasis rubra pilaris. *J Am Acad Dermatol*. 2018;79(3):487-494. doi:10.1016/j.jaad.2018.02.034

34. Ring NG, Craiglow BG, Panse G, et al. Histopathologic findings characteristic of CARD14-associated papulosquamous eruption. *J Cutan Pathol*. 2019. doi:10.1111/cup.13633

35. Mellett M, Meier B, Mohanan D, et al. *CARD14* gain-of-function mutation alone is sufficient to drive IL-23/IL-17-mediated psoriasiform skin inflammation in vivo. *J Invest Dermatol*. 2018;138(9):2010-2023. doi:10.1016/j.jid.2018.03.1525

36. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? a systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol*. 2012;66(3):369-375. doi:10.1016/j.jaad.2011.01.022

37. Regeneron Pharmaceuticals, Inc. *A phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients With Moderate to Severe Atopic Dermatitis* [clinical study report No. R668-AD-1334; confidential internal manufacturer's report]. Regeneron Pharmaceuticals, Inc; 2016.