An Open-Label Proof-of-Concept Study of Ixekizumab in the Treatment of Pyoderma Gangrenosum

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Abstract

INTRODUCTION Ixekizumab, a monoclonal antibody (MAB) targeting interleukin-17 (IL-17), represents a potential treatment avenue for pyoderma gangrenosum (PG) patients unresponsive to first-line therapies. The objective of this study was to determine the safety and efficacy of ixekizumab in PG. **METHODS** An open-label proof-of-concept study was performed on a cohort of 5 PG patients. Patients were intended to receive subcutaneous ixekizumab injections at baseline (160 mg) and 2-week intervals (80 mg) for 12 weeks. Objective measures including a 5-point investigator global assessment (IGA) and patient-reported outcomes (PRO) were assessed at baseline and completion. NanoString profiling was performed in pre- and post-treatment biopsy samples to assess for differential expression of genes associated with inflammation and immunity. **RESULTS** 5 patients were screened and consented, and 4 were enrolled. Unfortunately, the trial was terminated early due to serious adverse events in 3 patients. Total treatment duration was variable among patients (12, 6, and 2 weeks). Outcome assessments were performed at baseline and completion (mean (std dev)). Objective measures showed average increases in IGA (+0.33 (0.58)) and total ulcer surface area (SA) (+9.01 (7.27) cm^2). No patients achieved target ulcer closure. PRO showed average decreases in patient global assessment (PGA) (-1.67 (2.08)), patient pain visual analog scale (VAS) (-0.83 (1.04)), and dermatology life quality index (DLQI) (-2.25 (6.55)). NanoString identified differential expression of 5 genes in response to ixekizumab treatment. **CONCLUSIONS** Due to the small sample size and early termination of this trial, the utility of ixekizumab and IL-17 inhibition in PG remains uncertain.

Keywords: pyoderma gangrenosum, ixekizumab, neutrophilic dermatoses.

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INTRODUCTION

Pyoderma gangrenosum (PG) is an inflammatory cutaneous dermatosis associated with significant pain, debility, and detrimental effects on various quality of life domains.[1-2] PG lesions commonly present on the anterior lower extremities; key features suggestive of this diagnosis include an irregularly-shaped area of central ulceration, an undermined ulcer edge, and surrounding erythema.[3-6] PG often occurs alongside 1 or more comorbid systemic diseases that significantly impact patient outcomes; examples include hematologic malignancies, monoclonal or polyclonal gammopathies, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and vasculidities.[3-8] Thus, PG has profound influence on both survival and quality of life.[1-2,8]

PG is thought to be driven by aberrant immune system function and auto-inflammation. Although the precise pathophysiology remains to be determined, previous studies have identified neutrophils, T cells, and inflammatory cytokines and chemokines as potential mediators.[9-11]

PG medications are primarily immunosuppressive in nature, and corticosteroids or cyclosporine are often the initial treatment of choice.[12-14] Other options include tumor necrosis factor (TNF) inhibitors, various interleukin (IL) inhibitors, dapsone, mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIG), azathioprine, methotrexate, phosphodiesterase-4 (PDE-4) inhibitors, and Janus kinase (JAK) inhibitors.[12,14] Despite these various off-label treatments, there remains a lack of regulatory agency-approved treatments for PG, and new therapeutics are needed.[12,14]

IL-17 is a downstream pro-inflammatory cytokine thought to play a particular role in the autoinflammatory pathophysiology of PG.[9-11] This hypothesis is supported by molecular studies.[9,11] In a study by Marzano et al., IL-17 and its associated receptor were found to be overexpressed in skin biopsies from the undermined edge of PG ulcers.[9] In addition, Ortega-Loayza et al. found differential expression of IL-17 in perilesional PG skin biopsies compared to samples of healthy skin in control patients.[11] These studies support the plausibility of specifically targeting IL-17 for inhibition in PG, to block its pro-inflammatory effects.

Monoclonal antibodies directed specifically against IL-17 include ixekizumab, secukinumab, and brodalumab. These medications represent a potential treatment avenue for patients with severe PG who are unresponsive to first-line therapies.[12,14]

We first initiated this trial in 2017 as the first pilot study to investigate the safety and efficacy of ixekizumab in PG patients. Since the termination of this trial in 2018, IL-17 inhibitors have demonstrated potential effectiveness for PG in the literature; however, findings are largely limited to case reports and small series.[12,14-24] Here, we report the findings of our early trial, including an analysis of gene expression signatures in PG ulcer biopsy samples in response to ixekizumab treatment.

METHODS

Research Hypothesis

The aim of this study was to provide insights into the effects of IL-17 inhibition in PG, by assessing the safety and efficacy of ixekizumab in a small cohort of PG patients unresponsive to first-line therapies.

Primary Objective

The primary objective of this study was to determine the efficacy of ixekizumab for treatment of PG target ulcers based on changes in 5-point investigator global assessment (IGA) scores.

Secondary Objective

The secondary objectives of this study included further assessment for clinical improvements in PG target ulcers based on the frequency of ulcer closure and changes in total ulcer surface area (SA) measurements, as well as the evaluation of changes in patient-reported outcomes (PRO), including patient global assessment (PGA), patient pain perception using a 10-point visual analog scale (VAS), and patient quality of life using the dermatology life quality index (DLQI).

Study Design

We conducted a Phase II open label study in 5 patients with PG. The intended total treatment duration was 12 weeks, with ixekizumab doses scheduled at baseline and 2-week intervals, and a final follow-up at 16 weeks.

Recruitment, Eligibility, and Randomization

Patients were recruited from within The Ohio State University Wexner Medical Center Department of Dermatology. Identified PG patients who had received inadequate benefit from first-line therapies were screened. Patients meeting inclusion and exclusion criteria (Table 1) were eligible for enrollment. Enrollment occurred in 2017 and 2018. At the time, lacking a validated system for diagnosis and eligibility, we proceeded with adjudicative dermatologist review of patients with the features described below.[3-6,25]

Table 1. *Eligibility criteria.*

Inclusion Criteria
Clinical diagnosis of classic PG for at least 3 months, as determined by the investigator and an external reviewer, on the basis of results from clinical, histological, and laboratory assessments PG ulcer characterized by (a) AND 3/5 features of (b) OR 2/5 features of (b) with support from 1 of the conditions in (c): a. Stable or increasing size within the 2 months preceding screening (per patient report or provider documentation) b. Features such as violaceous border, undermining, cribriform scarring, pustules, and peristomal location c. Identifiable secondary systemic condition such as IBD, arthritis, MGUS, noncancerous hematologic disease, Streptococcal carriage, sequelae of levamisole-tainted cocaine use, or XLA PG target ulcer with SA $\geq$ 2 cm^2 and $\leq$ 200 cm^2 at screening Initial IGA of 3 or higher on a 5-point scale (0-4)
Exclusion Criteria
Any condition or situation that may compromise the ability to give written informed consent, may put the patient at significant risk, may jeopardize the patient's safety after exposure to the study drug, may confound the study results, or may interfere significantly with the patient's participation in the study (e.g., psychiatric illness, severe alcoholism, drug abuse) History of malignancy within 2 years of screening (not including carcinoma in-situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin) History of seropositivity for HIV antibody; active or carrier status of HBV (HBsAg positive or anti-HBc positive with negative anti-HBs); active HCV (not treated or not cleared spontaneously, as confirmed by HCV PCR) Systemic infection (excluding wound colonization) requiring oral antibiotics within 2 weeks of Day 0

History of any of the following treatments:

a. Anti-TNF or other biologic therapies within 5 half-lives of screening
b. Changes (addition, discontinuation, or dose adjustments) in immunosuppressive medications (including cyclosporine, azathioprine, methotrexate, MMF, apremilast, dapsone, or corticosteroids) within 2 months of Day 0
c. Systemic corticosteroids > 20 mg daily (prednisone or equivalent) within 8 weeks of Day 0, or dose adjustments within 8 weeks of Day 0 (steroid tapers permitted per principal investigator discretion)
d. Intralesional corticosteroids within 8 weeks of Day 0 (topical immunomodulators permitted)
e. Wound debridement within 2 weeks of Day 0 (dressing changes permitted per investigator discretion)
f. Systemic antibiotics within 2 weeks of Day 0
g. Live attenuated vaccines within 3 months of Day 0 or live seasonal influenza or H1N1 vaccines within 2 weeks of Day 0 (recombinant and killed vaccines permitted)
h. Hyperbaric treatment within 4 weeks of Day 0
i. Investigational drug or device within 30 days or 5 half-lives of Day 0 (whichever is longer)
j. Prior exposure to ixekizumab
k. Concomitant medications used to treat PG within 5 half-lives of the study

Additional treatments (not described above) should be maintained at a stable dose

Major general surgery within 3 months of screening or anticipated general surgery during the study period

Failure to have any stabilization or response with previous use of cyclosporine or systemic corticosteroids for PG (indicative that the disease may not be PG)

Study Intervention

The intervention consisted of subcutaneous injections of ixekizumab. All enrolled patients were intended to receive the intervention; no comparator group was utilized. Patients, their physicians, and the primary investigator were aware of the treatment protocol. Patients provided written consent prior to their enrollment in the study.

The trial was intended to last for a total of 16 weeks, with patients receiving their first ixekizumab injection on "Day 0" (160 mg), followed by 80 mg injections every 2 weeks, for 12 weeks total. Baseline skin biopsies were performed at Day 0 (baseline), and completion skin biopsies were planned to be performed at 16 weeks (completion). In addition, interval data collection was planned to occur every 2 weeks, starting at Day 0 (baseline) and continuing until 16 weeks (completion). Due to unanticipated adverse events and early trial termination, the time of completion was variable across patients; this issue is discussed further in the results below.

Additional non-immunosuppressive and non-investigational therapies were permitted (at physician discretion), provided that the therapies had no history of association with progressive multifocal leukoencephalopathy (PML). Antibiotics were permitted, as needed, for evidence of superinfection (positive culture results, malodor, green discharge, etc.). In addition, patients were monitored for toxicities and adverse events by the principal investigator throughout the study duration.

Finally, NanoString nCounter, a gene profiling assay, was performed on both baseline and completion corollary skin biopsy samples for each patient.[26] Formalin-fixed peri-wound tissue was processed, and RNA was extracted and hybridized using methods consistent with NanoString nCounter manufacturer protocols.[26] NanoString utilizes hybridization technology to provide quantitative data on the differential expression of selected genes of interest in tissue samples; in this analysis, we targeted 578 genes involved in inflammation and immunity.[26]

Outcome Measures

Baseline assessments included 5-point IGA for the target ulcer, total ulcer SA (target and additional ulcers) (cm^2), PGA, 10-point pain VAS, and DLQI.

The primary endpoint was the proportion of patients treated with ixekizumab who achieved a 2-point reduction in the 5-point IGA for the target ulcer from baseline to completion. Secondary endpoints included frequency of closure of target and additional ulcers, change in total ulcer SA, and changes in PRO including PGA, 10-point pain VAS, and DLQI.

Exploratory endpoints included evaluation of calculated scoring metrics (IGA x ulcer SA) and changes in inflammatory biomarkers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), absolute neutrophil count (ANC), total leukocyte count (TLC), serum IL-1, IL-6, IL-8, and TNF) and serum biomarkers (perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) in patients with IBD, anti-streptolysin-O antibodies (ASO) in patients with Streptococcus-driven disease, and levels of monoclonal and polyclonal proteins in patients with monoclonal gammopathy of undetermined significance (MGUS) and elevated immunoglobulin A (IgA) levels).

Sample Size

Five patients were screened and consented. One patient developed Ramsay-Hunt syndrome during the screening period. Ultimately, 4 patients met the criteria and were enrolled. Further recruitment was halted due to adverse events that occurred in enrolled patients.

Statistical Analysis

Primary and secondary objectives were analyzed using absolute differences in scores and ulcer measurements from baseline to completion. NanoString provided quantitative gene expression counts for biopsy tissue samples at baseline and completion, and these results were analyzed using paired t-tests with a significance level of $p \leq 0.05$.

RESULTS

Four patients (3 males, 1 female) were enrolled in the study. On average, patients were 49.40 (15.50) years of age with a disease length of 3.80 (3.49) years (mean (std dev)). PG comorbid conditions included MGUS (3 patients), X-linked agammaglobulinemia (XLA) (1 patient), IgA vasculitis (1 patient), and presumptive Crohn's disease (CD) (1 patient). All patients had received various previous PG treatments, with inadequate benefit (Table 2).

Table 2. *Characteristics of consented patients.*

Patient ID	Age	Sex	PG Comorbid Condition(s)	Disease Length (Years)	Previous Treatments	Enrollment Status
1	62	M	MGUS	2	Cyclosporine Gevokizumab Prednisone RA-18C3	Yes
2	23	M	XLA	2	Gevokizumab Prednisone	Yes

3	55	F	MGUS Chronic Strep Carriage	2	Debridement Prednisone Vein ablation	Yes
4	49	F	MGUS IgA vasculitis	3	Dapsone Debridement Fluocinonide MMF Silver-sulfadiazine	No[a]
5	58	M	Presumptive CD[b]	10	Collagen/silver dressings Debridement Hyperbaric treatment Mafenide cream Skin grafting	Yes

Table 2 Legend: *a. screened and consented but not ultimately enrolled due to development of Ramsay-Hunt syndrome; b. based on Prometheus gene expression testing.*

One patient (Patient 1) completed the full 12-week treatment protocol with a final follow-up at 16 weeks. The trial was terminated for 2 patients (Patients 3 and 5) at 6 weeks, and 1 patient (Patient 2) was lost to follow-up after 2 weeks. Adverse events included sepsis requiring hospitalization (2 patients) and infection-related hospitalization for a comorbid condition (1 patient). There were no deaths in the study.

Data (mean (std dev)) was collected at baseline (4 patients) and completion (variable) (Table 3). Regarding the primary endpoint, the average IGA increased from baseline (3.25 (0.50)) to completion (3.67 (0.58), 3 patients). Regarding secondary endpoints, no patients achieved ulcer closure at completion. The average total ulcer SA increased from baseline (15.18 (9.35) cm^2) to completion (24.19 (16.22) cm^2, 4 patients). PRO measures showed a decrease in average PGA from baseline (6.00 (3.56)) to completion (5.33 (2.08), 3 patients), a decrease in average pain VAS from baseline (6.38 (2.50)) to completion (6.00 (2.00), 3 patients), and a decrease in average DLQI from baseline (10.50 (7.14)) to completion (8.25 (6.08), 4 patients).

Table 3. *Baseline and completion data for enrolled patients.*

Table 3a. *IGA*.

	Patient 1[a]	**Patient 2[b]**	**Patient 3[c]**	**Patient 5[c]**	**Mean (Std Dev)**
Baseline	3	3	3	4	3.25 (0.50)
Completion	3	N/A	4	4	3.67 (0.58)
Change	0	N/A	+1	0	+0.33 (0.58)

Table 3b. *Total ulcer surface area*.

	Patient 1[a]	**Patient 2[b]**	**Patient 3[c]**	**Patient 5[c]**	**Mean (Std Dev)**
Baseline	14.56	2.28	23.40	20.48	15.18 (9.35)
Completion	19.38	3.96	41.40	32.00	24.19 (16.22)
Change	+4.82	+1.68	+18.00	+11.52	+9.01 (7.27)

Table 3c. *PGA*.

	Patient 1[a]	**Patient 2[b]**	**Patient 3[c]**	**Patient 5[c]**	**Mean (Std Dev)**
Baseline	3	3	8	10	6.00 (3.56)
Completion	3	N/A	7	6	5.33 (2.08)
Change	0	N/A	-1	-4	-1.67 (2.08)

Table 3d. *Pain VAS.*

	Patient 1[a]	**Patient 2[b]**	**Patient 3[c]**	**Patient 5[c]**	**Mean (Std Dev)**
Baseline	6	5	10	4.50	6.38 (2.50)
Completion	6	N/A	8	4	6.00 (2.00)
Change	0	N/A	-2	-0.50	-0.83 (1.04)

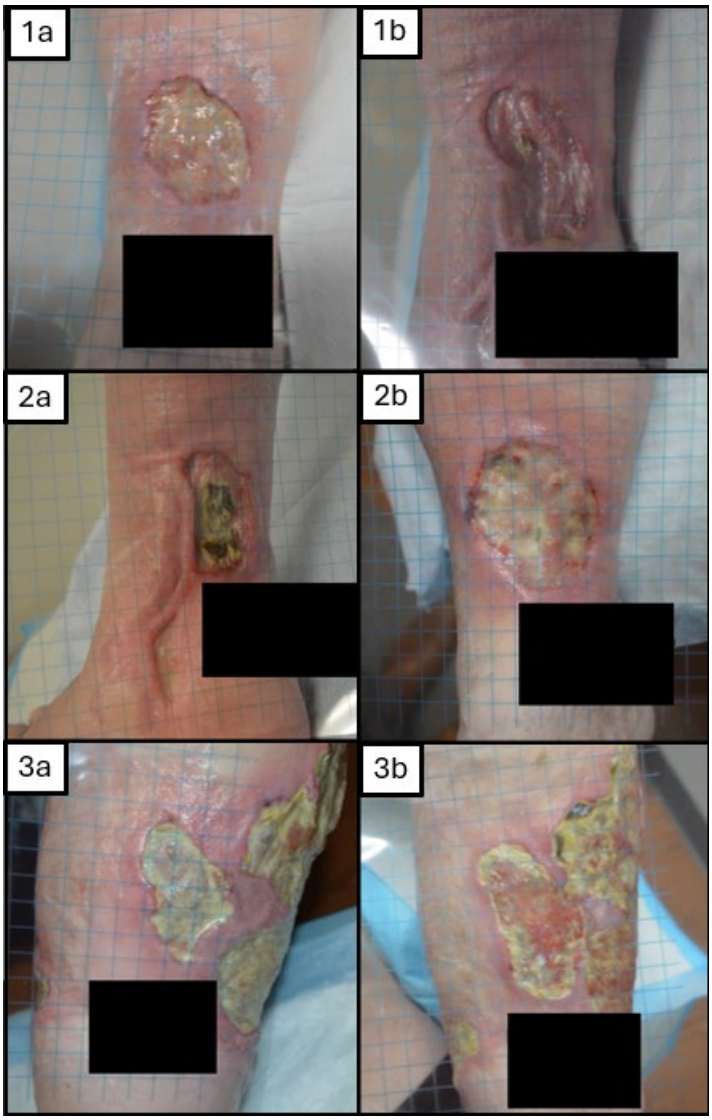
Table 3e. *DLQI.*

	Patient 1[a]	**Patient 2[b]**	**Patient 3[c]**	**Patient 5[c]**	**Mean (Std Dev)**
Baseline	6	3	15	18	10.50 (7.14)
Completion	7	3	17	6	8.25 (6.08)
Change	+1	0	+2	-12	-2.25 (6.55)

Table 3 Legend: *a. completion at 16 weeks; b. completion at 2 weeks; c. completion at 6 weeks.*

Images of target ulcers for 3 patients (Patients 1, 3, and 5) at baseline and completion are included in Figures 1a-3a and 1b-3b, respectively. All 3 patients later achieved ulcer healing on infliximab (2) and adalimumab (1).

Figures 1a-3b. *Target ulcers for 3 separate patients at baseline ("a" figures) and completion ("b" figures).*



NanoString profiling was performed on skin biopsy samples at baseline and completion (Table 4).[26] Quantitative gene expression signatures for 578 targeted genes showed significant differential expression of 5 genes in response to ixekizumab treatment, including cluster of differentiation 209 (CD209), cluster of differentiation 164 (CD164), killer cell lectin-like receptor A1, pseudogene (KLRAP1), lymphotoxin alpha (LTA), and leukocyte immunoglobulin-like receptor B4 (LILRB4). Mean CD209 and LTA counts decreased from pre-treatment to post-treatment, and mean CD164, KLRAP1, and LILRB4 counts increased from pre-treatment to post-treatment (Figure 4). Differential expression levels for autophagy related 16 like 1 (ATG16L1) and leukotriene B_4 receptor 2 (LTB4R2) did not reach statistical significance.

Table 4. *Gene expression signatures from ulcer biopsy samples.*

Gene of Interest	Encoded Protein and Significance[a]	Pre-Treatment Expression[b]	Post-Treatment Expression[b]	Post/ Pre	p[c,d]
CD209	• Encodes a C-type lectin on dendritic cells[27] • Promotion of pathogen recognition, cell adhesion[27]	1229.63 (171.47)	998.25 (143.47)	0.81	**0.003**
CD164	• Encodes an adhesive surface glycoprotein[28] • Participation in negative regulation of hematopoietic cell proliferation[28]	2682.89 (647.04)	4472.25 (1534.65)	1.67	**0.020**
KLRAP1	• Pseudogene (non-coding) • Receptor family associated with signal transduction, NK cell signaling[29]	3.58 (3.55)	6.25 (3.86)	1.75	**0.032**
LTA	• Encodes a cytokine in the TNF family[30] • Roles in inflammation, host immune response to pathogens[30]	1195.01 (185.90)	886.25 (250.08)	0.74	**0.034**
LILRB4	• Encodes a LILR expressed on monocytes and dendritic cells[31] • Negative regulation of the immune response[31]	1658.33 (218.64)	2143.00 (300.84)	1.29	**0.047**
ATG16L1	• Encodes a protein involved in autophagy[32] • Contributes to intracellular lysosomal degradative processes[32]	875.98 (110.07)	636.75 (253.87)	0.73	0.051
LTB4R2	• Encodes a receptor for LTB_4 and 12-HHT, highly expressed in intestinal mucosa and epithelial cells[33] • Intracellular signaling, chemotaxis, mucosal proliferation, keratinocyte migration[33]	334.17 (139.67)	226.50 (40.52)	0.68	0.053

Table 4 Legend: *a. the listed roles for each gene are not exhaustive, but rather, focus on those with potential relevance to PG; b. mean (standard deviation); c. significance threshold $p < 0.05$,* ***bold text in column 6 indicates statistically significant result****; d. paired t-test.*

Figure 4. *Gene expression signatures from ulcer biopsy samples.*

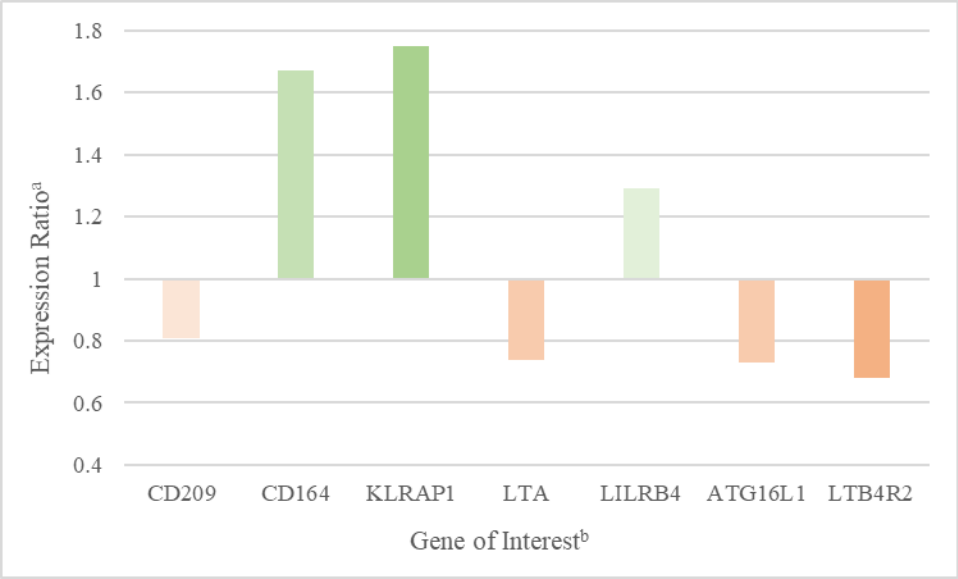


Figure 4 Legend: *a. Expression ratios were determined using the following formula: post-treatment expression level / pre-treatment expression level. Green indicates an increase in expression of the corresponding gene following ixekizumab treatment, orange indicates a decrease in expression of the corresponding gene following ixekizumab treatment; darker colors indicate a greater net change in expression from pre-treatment to post-treatment; b. the significance of each gene's encoded protein is displayed in Table 4.*

DISCUSSION

Ixekizumab is well-demonstrated to be safe and effective for inflammatory disorders including psoriasis and psoriatic arthritis.[34-35] However, less clarity exists regarding the application of ixekizumab to PG. This trial, initiated in 2017, was the first to examine the safety and efficacy of ixekizumab in a cohort of PG patients. Unfortunately, severe adverse events prompted early termination of the trial in 2018. Since then, several cases demonstrating ixekizumab efficacy in PG have been published in the literature, with no associated adverse events.[12,14-17] However, interestingly, Pollack et al. reported a case of ixekizumab-induced PG in a psoriasis patient; the precise mechanism underlying this reaction is not known.[12,14,36]

Similar to ixekizumab, secukinumab and brodalumab are IL-17 inhibitors that have demonstrated initial promise in treating PG.[12,14,18-24] Varying degrees of response have been reported in patients treated with secukinumab, with some achieving complete ulcer closure, and others experiencing persistent or worsening disease activity.[12,14,18-22] Reports on brodalumab use in PG are few; however, ulcer healing has been described in 3 such patients.[12,23-24] As with ixekizumab, secukinumab and brodalumab have been identified as culprits of drug-induced PG.[12,14,37-41]

In addition to paradoxical IL-17 inhibitor-induced PG, prior studies have identified a paradoxical association between IL-17 inhibition and IBD.[42-43] A Phase II trial evaluating the use of brodalumab in patients with CD resulted in early termination due to the exacerbation of disease in the intervention group.[44] In patients taking ixekizumab, secukinumab, and brodalumab, the rate of IBD occurrence has been described as 2.4 per 1000 patient-years.[43] Recognition of this risk and close monitoring for gastrointestinal symptoms are particularly important for PG patients, in whom comorbid CD and ulcerative colitis (UC) are common.[3-8]

Three patients in this study eventually achieved ulcer healing with biologics (infliximab and adalimumab) targeting TNF, an inflammatory cytokine that has also been implicated in the pathogenesis of PG, and lies upstream in the inflammatory cascade to IL-17.[9-12] In addition, 1 of the patients with concomitant MGUS healed on IVIG therapy, providing credence for treating PG patients with therapies that most closely address their underlying

disease process.[9-10,12]

The differential expression of genes related to neutrophil and cytokine function, the complement pathway, and cell adhesion molecules (CAM) have been demonstrated in the perilesional dermal tissue of PG patients in comparison to control patients.[11] Our NanoString results revealed significant differential expression of cluster of differentiation 209 (CD209), cluster of differentiation 164 (CD164), killer cell lectin-like receptor A1, pseudogene (KLRAP1), lymphotoxin alpha (LTA), and leukocyte immunoglobulin-like receptor B4 (LILRB4) in pre-treatment versus post-treatment skin biopsy samples. These genes are associated with various pathways including, but not limited to, cell adhesion and pathogen recognition (CD209), hematopoiesis (CD164), natural killer (NK) cell signaling (KLRAP1), and promotion or negative regulation of inflammatory and/or immune responses (LTA, LILRB4).[27-31] Although not statistically significant, we found a decrease in expression of autophagy related 16 like 1 (ATG16L) in response to ixekizumab. Notably, ATG16L has been described in association with CD.[32] It is important to appreciate sources of heterogeneity in our small cohort when approaching these results, including the wide range of ixekizumab treatment periods (2-12 weeks), variations in baseline gene expression counts, and diverse patient profiles (comorbid conditions, differing duration of disease). Gene expression profiling should be utilized in future PG trials, as it may offer additional insights into PG pathophysiology, underlying mechanisms of trial medications, and PG disease-driving pathways not targeted by current medications.[11,26]

Patient 2 (with underlying XLA) is the only patient in this study who has not achieved ulcer healing since the trial period. Although this patient did not adhere to IVIG during the trial period, he has since been adherent, without the healing of ulcerations. It is possible that the mechanism underlying chronic ulcerations in XLA patients differs from that of PG patients with other concomitant systemic diseases.[45] Of note, Helicobacter species (*H. bilis, H. cinaedi*) are associated with cutaneous ulcers resembling PG in this population.[45-48] Patient 2 has undergone cultures and multiple molecular tests in an effort to identify *H. bilis*, as well as a year of empiric therapy to cover this organism, without significant disease improvement. It is important to recognize that allowing the inclusion of XLA as an underlying disease may have significantly diluted our potential for a consistent baseline disease state in our small cohort.

Our results are limited by the small patient sample size and the early termination of the trial, resulting in insufficient interval and completion data and an inability to investigate exploratory endpoints. The primary endpoint (proportion of subjects achieving a 2-point reduction in the 5-point IGA) was observed in 0/4 enrolled patients; in fact, IGA scores increased from baseline to completion. Similarly, objective secondary endpoints (frequency of ulcer closure and change in total ulcer SA) revealed stable or worsening findings. On average, PRO data showed decreases in all scores (PGA, pain VAS, DLQI) from baseline to completion.

Our cohort consisted of 5 patients with refractory PG and comorbid PG conditions who were at high risk for complications at baseline. Infectious diseases and the sequelae that follow are a challenge in this high-risk patient population, and may prohibit the continuation of experimental trials, as seen in this study. In fact, Patient 4 developed complications (Ramsay-Hunt syndrome) before the trial began, and thus, did not receive any doses of ixekizumab. Three of the enrolled patients developed severe infectious sequelae requiring hospitalization(s) throughout the study period, and 2 were found to have sepsis, with negative blood cultures. One of these patients had a significantly elevated TLC (> 60,000) on multiple occasions, despite repeatedly negative cultures. Fortunately, no deaths occurred during the study.

In the absence of regulatory agency-approved treatments for PG, IL-17 inhibition is one of many potential mechanistic targets that warrants further study.[9-12,14] Currently, there is a paucity of ongoing PG clinical trials, likely attributable to the challenges associated with PG as an incompletely understood disease process, and PG patients as an exceedingly high-risk population. To address these challenges, areas in need of further study include improved detection and diagnosis of PG beyond subjective clinical assessments, as well as implementation of standardized eligibility criteria for future PG clinical trials.[3-6,25] In addition, in order to evaluate trial results, agreement among dermatologists regarding appropriate PG outcome measures is needed, such as the development of specific instruments to evaluate PG severity and quality of life.[1-2,25]

CONCLUSIONS

Due to the early termination of this trial, the effect of ixekizumab and IL-17 inhibition in PG remains uncertain. While multiple adverse events were detected, necessitating early study closure, it is unclear whether these events were attributable to the study drug or to the extremely high-risk nature of the patient population. Future studies should evaluate IL-17 inhibition in PG cautiously, given the mixed data on response and safety.

Considering the multiple adverse events reported in this trial, further caution should be exercised in inclusion criteria, including evaluations of prior hospitalizations, sepsis, and infections.

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Conflicts of Interest: Funding for this trial was obtained by Benjamin H. Kaffenberger, MD from Eli Lilly and Company. Additionally, Dr. Kaffenberger has received: grants from InflaRx, Merck, Biogen, BMS, and Janssen; consulting fees from Elsevier, Eli Lilly, Novocure, and Novartis; and payment for expert testimony related to pyoderma gangrenosum.

Trial Registration: NCT03137160 https://classic.clinicaltrials.gov/ct2/show/NCT03137160

Abbreviations

ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
ASCA	Anti-saccharomyces cerevisiae antibodies
ASO	Anti-streptolysin-O antibodies
ATG16L1	Autophagy related 16 like 1
CAM	Cell adhesion molecules
CD	Crohn's disease
CD164	Cluster of differentiation 164
CD209	Cluster of differentiation 209
CRP	C-reactive protein
DLQI	Dermatology life quality index
ESR	Erythrocyte sedimentation rate
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
IgA	Immunoglobulin A
IGA	Investigator global assessment
IL	Interleukin
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
KLRAP1	Killer cell lectin-like receptor A1, pseudogene
LILRB4	Leukocyte immunoglobulin-like receptor B4
LTA	Lymphotoxin alpha
LTB_4	Leukotriene B_4

LTB4R2	Leukotriene B_4 receptor 2
MAB	Monoclonal antibody
MGUS	Monoclonal gammopathy of undetermined significance
MMF	Mycophenolate mofetil
NA	Not applicable/data unavailable
NK	Natural killer
p-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PCR	Polymerase chain reaction
PDE-4	Phosphodiesterase-4
PG	Pyoderma gangrenosum
PGA	Patient global assessment
PML	Progressive multifocal leukoencephalopathy
PRO	Patient-reported outcomes
RA-18C3	Bermekimab
SA	Surface area
STD DEV	Standard deviation
STREP	Streptococcus
TNF	Tumor necrosis factor
TLC	Total leukocyte count
VAS	Visual analog scale
XLA	X-linked agammaglobulinemia, Bruton's agammaglobulinemia
12-HHT	12-hydroxyheptadecatrienoic acid

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