Targeted therapy with ixekizumab in pyoderma gangrenosum: A case series and a literature overview

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Key words: biologics; IL-17; ixekizumab; pyoderma gangrenosum; targeted therapy.

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis often associated with underlying systemic immune dysregulation including inflammatory bowel disease (IBD) and internal malignancies.[1] It typically presents in patients aged between 22 and 55 years.[1] Tender pustules or nodules that are initiated by trauma, called the pathergy phenomenon, break down to form necrolytic ulcerations with erythematous and undermined borders, typically on the lower extremities.[1]

The pathophysiology of PG is not well understood, but it is theorized to be an autoreactive immune response.[1] An imbalance between T helper 17 and regulatory T cells leads to neutrophilic infiltrate along with elevated levels of tumor necrosis factor-α, interleukin (IL) 1β, IL-1α, IL-8, IL-12, IL-15, IL-17, IL-23, and IL-36.[2,3] Elevation in the levels of IL-6, interferon γ, granulocyte colony-stimulating factor, and matrix metallopeptidase 9 have also been reported.[1] Immunostaining of the ulcer border has demonstrated overexpression of IL-23, a proinflammatory cytokine that induces differentiation and maintenance of T helper 17 cells.[1] In our case series, we report successful treatment of extensive PG with targeting the IL-17 pathway with ixekizumab monotherapy.

CASE SERIES

All patients initially presented and were recruited in an outpatient dermatology clinic setting (Table I). Treatment was initiated with ixekizumab at a loading dose of 160 mg subcutaneous injection followed by 80 mg every 2 weeks until week 12, then 80 mg every 4 weeks.

Abbreviations used:

IBD: inflammatory bowel disease
IL: interleukin
PG: pyoderma gangrenosum

Case 1

A 60-year-old man with metastatic renal cell carcinoma on cabozantinib had a 6-month history of tender ulcers on his left hand as previously described by our group.[4] The erythematous ulcerative lesions with undermined borders rapidly expanded after biopsy and were refractory to topical corticosteroids (Fig 1, *A*). Cutaneous malignancy was ruled out through biopsy. Cabozantinib was discontinued 4 weeks into ixekizumab initiation. The lesions improved on follow-up assessment at 10 weeks (Fig 1, *B*) and diminished at the end of the 12-week treatment period with subsequent discontinuation of ixekizumab. No adverse effects were noted.

Case 2

A 62-year-old man without significant medical history had 3 months duration of severely painful ulcers on the right shin and left leg, limiting his mobility to requiring a wheelchair (Fig 2). The ulcers had undermined borders with peripheral erythema (Fig 2, *A*). Biopsy showed an infiltrate of neutrophils and lymphocytes with neutrophilic nuclear dust.

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2023;37:49-53.
2352-5126

https://doi.org/10.1016/j.jdcr.2023.05.002

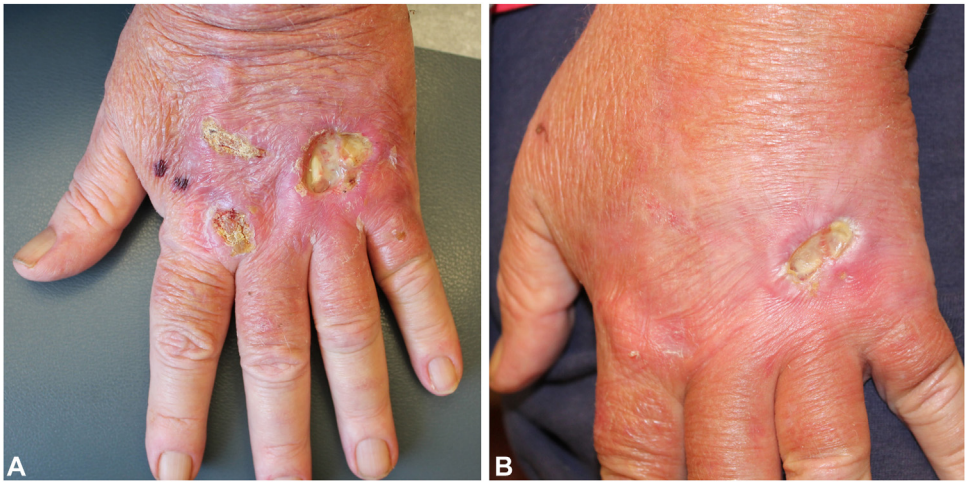

Fig 1. Pyoderma gangrenosum in patient 1 at (**A**) baseline with tender ulcer on the left hand and (**B**) after 10 weeks of treatment.

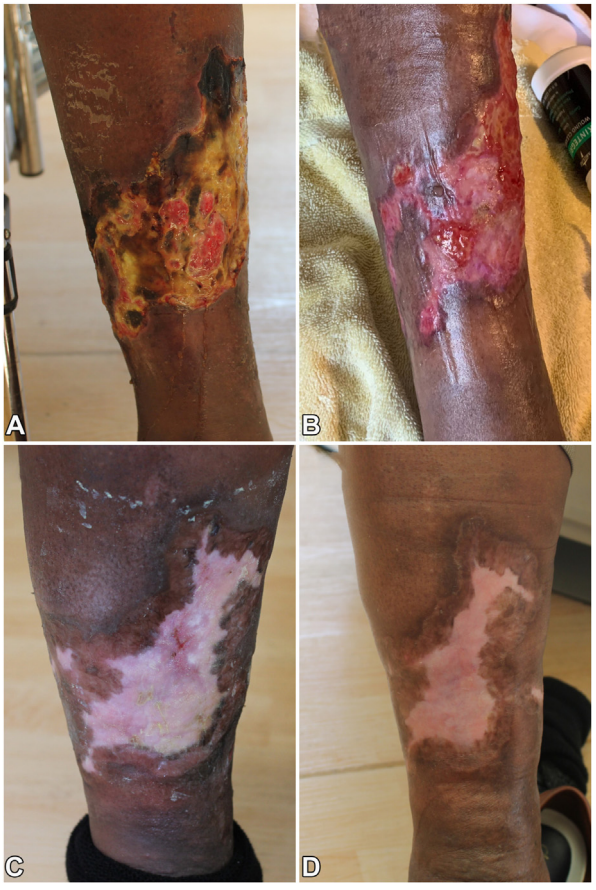

Fig 2. Pyoderma gangrenosum in patient 2 at (**A**) baseline with severely painful ulcers on the right shin, (**B**) after ixekizumab initiation, (**C**) after 24 weeks of treatment, and (**D**) 9 weeks after completion of 49 weeks of treatment.

Infection was excluded by gram, periodic acid–Schiff, and Grocott's methenamine silver stains. Rapid pain improvement was noted after initiation of ixekizumab (Fig 2, *B*). His right shin ulcer was nearly resolved at 12 weeks and ixekizumab was discontinued at 49 weeks after complete response (Fig 2, *C* and *D*). He remained clear after 100 weeks (23 months) of follow-up. No adverse effects were noted.

Case 3

A 26-year-old woman with history of hidradenitis suppurativa and prior episode of PG 6 years ago had a 1-month history of a tender papule on the lower portion of her right leg developing at the same site of her prior PG after SARS-CoV-2 infection (Fig 3, *A*). The papule rapidly ulcerated and was unresponsive to topical and intralesional corticosteroids (Fig 3, *B*). Biopsy and tissue culture from her prior episode of PG excluded bacterial, mycobacterial, and fungal infection. Diagnosis of PG was made and ixekizumab was initiated with rapid resolution and discontinuation at 47 weeks (Fig 3, *C* and *D*). Complete resolution was maintained at 68 weeks (16 months) follow-up. No adverse effects were noted.

Case 4

A 49-year-old woman presented with a painful ulcer on the left calf of 5 years duration (Fig 4). Biopsy showed neutrophilic inflammation. Infection was excluded by bacterial, fungal, and viral cultures. She was initially treated with cyclosporine for 18 months followed by mycophenolate mofetil for more than 1 year without improvement. At the time of initiation of ixekizumab, she was unable to work due to pain from her ulcer. Symptomatic improvement was appreciated after ixekizumab loading dose for 12 weeks followed by

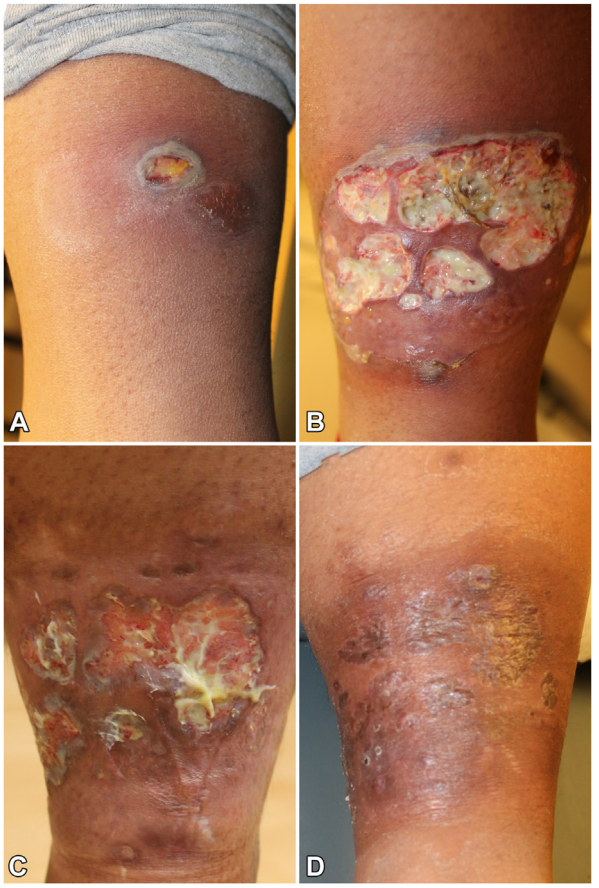

Fig 3. Pyoderma gangrenosum in patient 3 at (**A**) initial presentation with tender papule on the right calf 1 month prior to treatment, (**B**) initiation of treatment with multiple cribriform ulcers characterized by violaceous borders and undermined edges, (**C**) after 12 weeks of treatment, and (**D**) after 39 weeks of treatment.

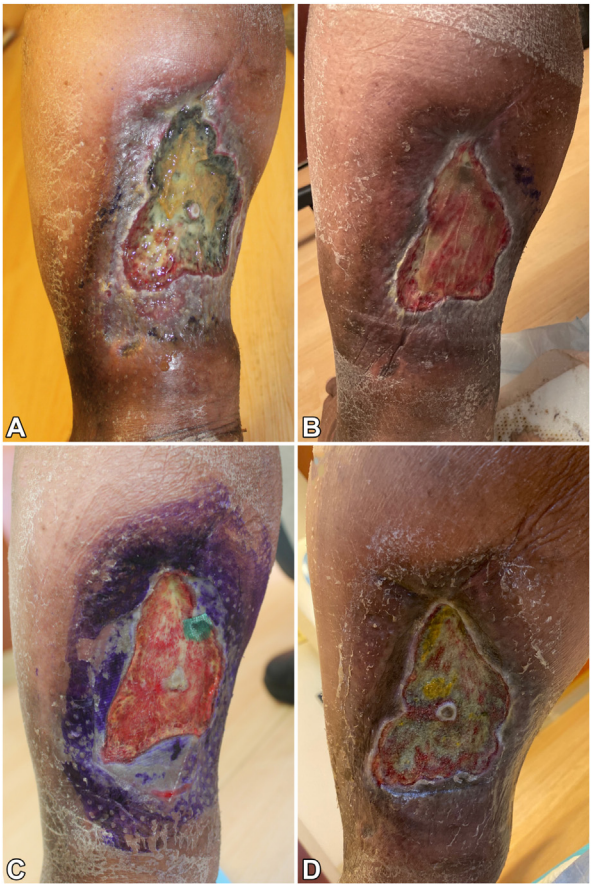

Fig 4. Pyoderma gangrenosum in patient 4 at (**A**) baseline with ulcer on the left calf, (**B**) after 4 weeks of treatment, (**C**) 16 weeks after treatment, and (**D**) 47 weeks after treatment.

the maintenance dosing (Fig 4, *B-D*). The patient returned to work at 30 weeks and has continued on treatment through 47 weeks. No adverse effects were noted.

DISCUSSION

As the underlying pathology of PG is due to immune dysregulation, immunosuppression is the current mainstay of treatment. Topical or intralesional corticosteroids are used to treat small, localized lesions. Systemic corticosteroids and cyclosporine are current first-line agents for rapidly progressive lesions. However, 1 multicenter randomized clinical trial of 121 patients showed less than 50% achieved remission at 6 months with either prednisolone or cyclosporine.[5] The majority experienced at least 1 therapy-induced adverse reaction, 66% and 68% in prednisolone and cyclosporine groups, respectively. Sulfasalazine, tacrolimus, thalidomide, azathioprine, minocycline, methotrexate, clofazimine, mycophenolate mofetil, and dapsone have also been used as monotherapy for the treatment of PG.[1] Intravenous immunoglobulin is an efficacious nonpharmacologic option with an attractive safety profile in the context of active infection or malignancy.[1] Due to concern of cost with repeated infusion, intravenous immunoglobulin is used generally early and subsequently transitioned to another medication.[1]

Biologics targeting specific cytokine mediators are reported to be safe alternative treatments. Inhibition of the tumor necrosis factor-α pathway through infliximab, etanercept, and adalimumab is an effective measure.[1,6] Skin biopsies of PG border have shown elevated expression of IL-23A in multiple cases.[7,8] Ustekinumab, an agent used for plaque psoriasis, has yielded multiple successful outcomes in PG cases without adverse effects.[9] In addition, IL-1 antagonists may be effective in treating recalcitrant PG.[1] O'Connor et al[10] reported 100% healing with anakinra, an IL-1 receptor antagonist that blocks the

Table I. Summary of patients with pyoderma gangrenosum treated with ixekizumab

Patient	Age (y)	Sex	Location	Medical history	Prior treatment	Ixekizumab treatment
1	60	M	Left dorsal hand	Metastatic renal carcinoma on cabozantinib	Topical corticosteroids	12 wk
2	62	M	Right shin, left calf	No significant medical conditions	No prior treatment	49 wk
3	26	F	Right calf	Hidradenitis suppurativa, PG 6 y prior, SARS-CoV-2	Topical and intralesional corticosteroids	47 wk
4	49	F	Left calf	No significant medical conditions	Cyclosporine for 18 mo, mycophenolate mofetil for over 1 y	47 wk, ongoing

F, Female; *M*, male; *PG*, pyoderma gangrenosum.

activity of IL-1α and IL-1β, in 2 patients with multiple comorbidities.

Here, we have described 4 cases of PG that resolved with IL-17 inhibition from ixekizumab without reported adverse effects. Other immunomodulating agents such as brodalumab (anti—IL-17R) and secukinumab (anti—IL-17A) are being proposed as available alternatives.[1] The predominance of neutrophils in PG makes inhibiting neutrophil migration through IL-17 a promising target. Secukinumab, a recombinant human IgG1 monoclonal antibody targeting IL-17A, was used in a 50-year-old woman with PG. Complete response was observed within 3 months and with no recurrence after an additional 2 months of maintenance therapy.[8] Brodalumab, an IL-17A receptor antagonist, has also yielded rapid resolution. In a 23-year-old man with acne conglobata, hidradenitis suppurativa, and a 2-year history of PG (Pyoderma gangrenosum, acne, and hidradenitis suppurativa syndrome) refractory to systemic corticosteroids, adalimumab, and adjuvant methotrexate therapy, a month of brodalumab resulted in rapid reduction with complete response without recurrence at 6 months.[11] A similar case with a successful outcome was seen at 3 months in a 52-year-old woman with 10-year history of recurrent PG and concomitant hidradenitis suppurativa refractory to systemic and intralesional corticosteroids and adalimumab.[11]

The mechanism of action of ixekizumab is similar to that of secukinumab in selective binding of IL-17A. An additional benefit is the avoidance of immunosuppression in the setting of solid tumor malignancy.[4] Interestingly, a case of paradoxical PG has been reported in patients with psoriasis each treated with ixekizumab and secukinumab.[12] This suggests intricate cytokine and immune regulatory interactions that have yet to be fully understood. The proposed mechanism is that inhibition of the IL-17 pathway upregulates the upstream IL-23 expression, as secukinumab-induced PG resolved with subsequent ustekinumab therapy.[13]

An open-labeled, prospective trial of ixekizumab in 4 patients with PG in 2018 was halted due to development of infection and sepsis in patients, complications not observed in our patients. Reported adverse effects of IL-17 inhibition include exacerbation of IBD.[13] However, there was no significant risk difference in the development of new-onset IBD with these agents in comparison with placebo in a meta-analysis of randomized clinical trials of anti—IL-17 agents (secukinumab, ixekizumab, and brodalumab).[14] A separate retrospective cohort analysis reported similar low incidence of IBD in cases of psoriasis treated with and without anti—IL-17 agents.[15] Further investigations and large clinical trials on biologics are still warranted to dictate standardized guidelines for the treatment of PG. This case series demonstrates that inhibition of the IL-17 pathway provides a rapid and effective option in the management of PG without underlying IBD. With a favorable safety profile compared to less targeted immunosuppressants, we aim to raise clinicians' awareness of targeted IL-17 pathway inhibition as a potential treatment for PG.

Conflicts of interest

None disclosed.

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