Recalcitrant Ulcerative Pyoderma Gangrenosum of the Leg Responsive to Tildrakizumab: A Case Report

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Abstract: Elevated levels of inflammatory mediators—including the interleukin IL-23—are implicated in the pathogenesis of pyoderma gangrenosum (PG), an autoinflammatory neutrophilic dermatosis characterized by rapidly enlarging, suppurative ulcers and cribiform scarring. Here, we present the first case report of significant response of isolated ulcerative PG with tildrakizumab, a biologic agent directed against the p19 subunit of IL-23, in an elderly woman with extensive treatment-refractory PG on her left leg. Tildrakizumab (100 mg subcutaneously at weeks 0 and 4, then every 8 weeks, and eventually increased in frequency to every 6 weeks), combined with acetic acid soaks each morning and chemical debridement every evening with 3% hydrogen peroxide, resulted in progressive decrease in ulcer size and depth, re-epithelialization, and recovery of sensory perception. This report describes the dramatic clinical response of ulcerative PG on the leg with tildrakizumab.

Keywords: interleukin-23, leg ulcers, pyoderma gangrenosum, biological drug, wound dressing

Introduction

Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis with an overall prevalence of 5.8 cases per 100,000 adults.1,2 It is most common in women and individuals over 70 years of age and is characterized by rapidly enlarging, suppurative ulcers that heal with cribiform scarring.2 Ulcerative PG, the most common subtype, classically manifests on the legs.1

The management of PG is challenging, as there is no management guideline based on clinical evidence or expert consensus.3,4 Topical and/or systemic medical therapy, analgesia, compression, and diligent wound care are indicated.1 Otherwise, treatment aims to minimize systemic inflammation, as the pathophysiology of PG—while multifactorial and poorly understood—1,5 is thought to involve inflammatory cytokines and signaling cascades including interleukin (IL)-23 and T-helper (Th)17 cell recruitment.6,7 However, there is no gold standard therapy, and more evidence is needed to establish a standardized treatment approach.

Tildrakizumab (ILUMYA®, Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA), a biologic agent indicated for the treatment of moderate-to-severe plaque psoriasis, is a monoclonal antibody that neutralizes IL-23 overexpression by targeting the p19 subunit of IL-23 to inhibit binding to the IL-23 receptor (IL-23p19 inhibitor).7 We present the first case report of treatment response to tildrakizumab of ulcerative PG of the leg previously unresponsive to standard therapies.

Case Report

An 85-year-old woman presented with extensive and severe sloughy, painful ulceration on most of her left leg. Her medical history included chronic skin ulcers since age 19, often secondary to trauma, and a family history of ulcerative cutaneous disease. In 2004, she developed an ulcer on the left shin that enlarged progressively and eventually extended to...
the calf. Unlike previous ulcers, it worsened despite attempts at debridement and daily wound care with normal saline and 10% povidone-iodine (Inadine™, Systagenix) dressings.

Initial wound swab cultures revealed moderate growth of ampicillin-, amoxicillin-, and penicillin-resistant Staphylococcus aureus, as well as tetracycline-resistant group B Streptococcus. After the patient was hospitalized for a urinary tract infection in August 2019 and the ulcer deteriorated, a subsequent wound swab culture confirmed Pseudomonas species. The patient recalled trialing a variety of oral antibiotics without success. Daily wound dressing changes were performed with gauze soaked with petrolatum or cadexomer iodine ointment (Iodosorb™, Smith & Nephew Healthcare, Watford, England, UK), povidone-iodine dressings, chlorhexidine acetate tulle (Bactigras™, Smith & Nephew Healthcare, Watford, England, UK), as well as silver and zinc oxide dressings. Surgical debridement was performed by scalpel.

Despite this treatment, the ulcer continued to worsen. A skin graft was considered but not performed due to potential complications involving the infected recipient site, and the patient also declined amputation. In January 2020, treatment was initiated with nonablative infrared laser (MLS Laser Therapy, Mphi 5 model, ASA Laser, Vicenza, Italy) 3 times a week and twice-daily wound cleansing with acetic acid soaks (household vinegar mixed with lukewarm boiled water approximating 0.3% acetic acid) for 30 minutes followed by exposure to natural sunlight for 10 minutes. The patient reported resolution of infection and significant improvement in the appearance of the wound with adjunctive non-ablative laser treatment from December 2019 to May 2020. This was ceased in June 2020 as no further benefit was apparent.

In March 2020, the patient was referred to a local dermatologist for ongoing ulcer management (Figure 1). The clinical presentation fulfilled all major and minor PARACELSUS criteria except extreme pain. PG was diagnosed based on the patient’s total PARACELSUS score of 17, which indicates a high likelihood of PG, and differentiates PG from venous leg ulcers. An excisional biopsy reported pseudoepitheliomatous hyperplasia, consistent with cellular proliferation from healing of the ulcer base. Lymphovascular involvement was absent. Histologic findings were confirmed by a senior dermatopathologist as consistent with PG.

The patient had severe derangement of renal function that precluded a trial of high-dose oral corticosteroid or cyclosporin. Treatment with 25 mg daily oral prednisolone and twice-daily topical betamethasone dipropionate ointment was initiated in March 2020. An adjunctive regimen of 400 mg oral pentoxifylline three times daily appeared to reduce venous stasis.

As systemic corticosteroid therapy did achieve significant improvement, in May 2020 oral dapsone 100 mg daily was commenced as the first steroid-sparing agent. The dose was reduced to 50 mg in June 2020 and subsequently discontinued due to treatment-emergent severe tremors. Oral cyclosporin 100 mg was commenced twice daily, with dose reduction to 50 mg twice daily due to severe known adverse effects in July 2020 followed by discontinuation in August due to limited efficacy. Blood investigations in late June 2020 revealed an erythrocyte sedimentation rate (ESR) of 81 mm/hour and a C-reactive protein (CRP) level of 69 mg/L. Oral minocycline 100 mg daily was used in July 2020 as a supplementary anti-inflammatory agent following disruption to the supply of pentoxifylline in Australia.

Figure 1 Ulcerative PG on the (A) anterolateral and (B) anteromedial aspects of the left leg on initial presentation, with extensive cribriform scarring and irregular overhanging borders.
In August 2020, subcutaneous tildrakizumab 100 mg was commenced, with a loading dose at week 4 followed by regular dosing every 8 weeks. Application of betamethasone dipropionate ointment continued daily following acetic acid soaks. Non-woven gauze and combine pads were applied overnight to absorb exudate. By October 20, both ulcer size and depth improved, with re-epithelialization (Figure 2). Light touch and pain perception were regained over the ulcer, which was previously largely anaesthetic. Considering this encouraging response to treatment, the tildrakizumab dosage was increased by shortening administration intervals to 6 weeks. In November 2020, prednisolone was discontinued due to the patient’s history of bacterial infection, and pentoxifylline was resumed, replacing minocycline.

In December 2020, acetic acid soaks were ceased and the fibrinous floor of the ulcer became excessively thickened, hampering re-epithelization and resulting in heaped-up wound edges (Figure 3). To address excess fibrin deposition, more rigorous daily wound care was initiated, including 3% hydrogen peroxide applied by non-woven gauze and deactivated by rinsing with water, complemented by fastidious daily debridement. The ulcer displayed noticeable re-epithelialization by January 2021. Simple debridement through daily wound care with betaine 0.1%/polyhexanide 0.1% solution (Prontosan® Wound Irrigation Solution, B. Braun) (BP) was initiated in late January 2021. The site was soaked in BP for 15–20 minutes each morning, followed by application of an antimicrobial silver dressing (Acticoat™ Flex 3, Smith & Nephew Healthcare). An outer dressing was added, comprising absorbent cellulose (Zetuvit® Plus, Hartmann AG) and combine pads. Over the following 6 weeks, the silver dressing was replaced every 3 days and reapplied during wound care on intervening days, along with BP. This regimen achieved dramatic clinical response by late February (Figure 4).

In March 2021, a malodorous yellow-green slough suspicious for *Pseudomonas aeruginosa* infection was present. Oral ciprofloxacin 500 mg was administered empirically twice daily for a week, and the infection subsequently resolved. ESR and CRP levels in April 2021 were 99 mm/hour and 25 mg/L, respectively, comparing favorably with these parameters approximately a year earlier.

As of September 2021, the wound was healing progressively from its edges (Figure 5) upon continuation of this combination therapy of tildrakizumab injections, oral pentoxifylline, and wound care. Further re-epithelialization was observed as of the last follow-up in March 2022 (Figure 6). No adverse effect has been reported to date.

![Figure 2](https://example.com/figure2.jpg) **Figure 2** Re-epithelialization and reduction in ulcer size at week 8 of tildrakizumab treatment on the (A) medial and (B) anterolateral aspects of the left leg.
Discussion

Several biologic agents targeting different cytokines have demonstrated at least some efficacy in PG.\textsuperscript{6,7,13–18} Because PG involves cutaneous neutrophilic infiltration and IL-23 overexpression, IL-23p19 inhibition could reasonably be expected to result in clinical improvement.\textsuperscript{6,7} Significant improvement was observed in 2 patients, a 59-year-old woman with refractory leg PG and a 43-year-old woman with peristomal PG, following treatment with the IL-23p19 inhibitor.
Two other cases of ulcerative PG of the leg successfully resolved within 4 months of treatment with guselkumab, another IL-23p19 inhibitor.\textsuperscript{21,22} A single case of successful treatment of penile PG with tildrakizumab was previously described, while Murrell and Sheriff (2021) reported a case of recalcitrant PG responsive to tildrakizumab and ustekinumab combination therapy.\textsuperscript{23} However, this is the first report of positive response to tildrakizumab monotherapy in recalcitrant ulcerative leg PG.

Figure 5 Re-epithelialization with bridging of advancing edges at week 55 of tildrakizumab treatment on the (A) anteromedial and (B) anterolateral aspects of the left leg.

Figure 6 Further improvement at week 82 of tildrakizumab treatment on the (A) anteromedial and (B) anterolateral aspects of the left leg. Although focal areas of impetiginization are prominent, there is obvious significant further re-epithelialization.
PG also presents as part of the neutrophilic autoinflammatory syndromes that feature constellations of disparate skin sites and manifestations, including pyogenic arthritis and acne (PAPA); acne and hidradenitis suppurativa (HS) (PASH); pyogenic arthritis, acne, and HS (PAPASH); and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO). In a case of PASH with an exacerbation of HS and leg PG following long-term stabilization on oral prednisolone, commencement of tildrakizumab enabled prednisolone dosage taper, although the PG component did not resolve. PG and HS can also present concurrently. Tildrakizumab has been useful in HS, where overexpression of IL-23 and bacterial biofilm formation may contribute significantly to pathogenesis. Importantly, our patient did not have PG as part of these syndromes. The presence of slough and nonviable tissue (in PG), as well as microbiome dysregulation (in PG and HS), may promote biofilm formation. This is associated with impaired epithelialization and the formation of granulation tissue, triggering an inflammatory response that impedes wound healing. We postulate that tildrakizumab may also have a secondary effect on biofilm colonies in PG. S. aureus may trigger Th1/Th17 responses, which are associated with biofilm formation and could exacerbate chronic infection. As IL-23 is required for the maintenance of Th17 cells, inhibition of IL-23 by tildrakizumab may additionally suppress these inflammatory host responses and hinder biofilm development in PG.

Interestingly, this patient experienced a marked improvement with acetic acid soaks, which may have helped prevent P. aeruginosa biofilm development. Diluted acetic acid is also effective against S. aureus and group B Streptococcus. Hydrogen peroxide, potassium permanganate, povidone-iodine, and silver nitrate soaks have all been reported useful as part of the conservative management of PG. Debridement by laser ablation has a role, and there is anecdotal evidence that nonablative laser is also beneficial. In our case, clinical improvement plateaued after several months of supportive treatment with this modality. Another option to consider would have been negative pressure wound therapy in combination with the above systemic anti-inflammatory and immunosuppressive therapies.

Over the course of treatment, excess fibrin deposition from inadequate debridement was the predominant factor hindering re-epithelialization. In PG, avoidance of overzealous debridement is recommended due to the risk of pathergy. However, judicious debridement removes necrotic tissue and fibrin, which in turn facilitates re-epithelialization.

**Conclusions**

This is the first case report of tildrakizumab treatment achieving a positive response in recalcitrant ulcerative leg PG, notably the most common PG subtype at its most common anatomical site. Our findings are consistent with recent case reports of other IL-23p19 inhibitors and suggest that incorporating IL-23 inhibitors such as tildrakizumab as part of the systemic treatment ladder for PG could be beneficial. More studies are needed to confirm our observations.

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