Emanuel Maverakis

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*Correspondence: Department of Dermatology, University of California Davis School of Medicine, 3301 C Street, Suite 1400, Sacramento, CA 95816 (e-mail: emaverakis@ucdavis.edu).

Abbreviations and Acronyms

CD2BP1 = CD2 binding protein 1

G-CSF = granulocyte colony-stimulating factor

IBD = inflammatory bowel disease

IFN- γ = interferon gamma

IL = interleukin

IVIG = intravenous immunoglobulin

MMP-9 = matrix metalloproteinase 9

PAPA = pyogenic arthritis, pyoderma gangrenosum and acne

PG = pyoderma gangrenosum

PSTPIP1 = proline-serine-threonine phosphatase-interacting protein 1

TNF = tumor necrosis factor

Effective Strategies for the Management of Pyoderma Gangrenosum

Heidi Goodarzi,¹ Raja K. Sivamani,¹ Miki Shirakawa Garcia,¹ Lisa N. Wehrli,^{1,2} Hilary Craven,¹ Yoko Ono,^{1,2} and Emanuel Maverakis^{1,2,*}

¹Department of Dermatology, University of California Davis School of Medicine Sacramento, California.

²Veterans Affairs Northern California Health Care System, Sacramento, California.

Background: Pyoderma gangrenosum (PG) is an inflammatory disease characterized by painful ulcerations. It is often associated with other systemic inflammatory diseases, especially inflammatory bowel disease (IBD) and autoimmune arthritis.

The Problem: PG does not have characteristic serologic or histologic features. Therefore, other potential causes such as malignancy, vasculitis, infection, and coagulation disorders should be ruled out. In addition, patients often have aggressive disease that is refractory to immunosuppressive therapy, but there is only a paucity of clinical data to help direct therapy.

Basic/Clinical Science Advances: There are several lines of evidence to support an immunologic etiology of PG. Although the pathogenesis is still not well understood, it is clear that PG is associated with the upregulation of several cytokines including interleukin 8 (IL-8), tumor necrosis factor (TNF), IL-1 β , IL-6, and interferon gamma, among many others. TNF and IL-1 β are of particular interest, because some biologic medications that target these cytokines have been effective in treating PG.

Clinical Care Relevance: Multiple drugs are available to help control PG. Biologics, intravenous immunoglobulin (IVIG), and conventional immunosuppressive drugs have been reported to be effective. Multidrug therapies should be considered for refractory cases.

Conclusion: PG is a complex inflammatory disease with multiple involved pathways. Anti-TNF agents and IVIG represent a significant advancement in treatment options. Since some biologic therapies are relatively new, their unknown long-term side effects should be taken into consideration.

BACKGROUND

BRUNSTING, GOECKERMAN, AND O'Leary coined the term *pyoderma gangrenosum* (PG) to describe a series of patients with recurrent ulcerations.¹ Although these original authors hypothesized an infectious etiology for PG, the disease is now considered an aberrant, possibly autoimmune response. It affects patients of all ages, especially those between 20 and 50 years. The classic lesions are painful, lower ex-

tremity ulcerations with raised erythematous and undermined borders that are red to purple in color (Fig. 1). In active lesions, macular erythema can exist peripherally to the undermined edge, or in place of it in less active lesions.

Typically, a PG lesion forms at the site of minor trauma as a tender inflammatory nodule or pustule that breaks down over time to create a putrid ulceration with excessive granulation tissue at its base. The

Figure 1. Lower extremity ulcerations with surrounding dark purple undermined borders. Granulation tissue and neutrophilic abscesses are present at the base of the ulcers. Small rim of erythema is seen peripherally to the undermining borders.

TARGET ARTICLES

1. Brooklyn TN, Dunnill MGS, Shetty A, Bowden JJ, Williams JDL, Griffiths CEM *et al.*: Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006; **55**: 505.
2. Meyerle JH, Cummins DL, Anhalt GJ, and Monahan T: Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; **157**: 1235.
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appearance of an ulcer in response to minor trauma is called *pathergy*, and this is a hallmark of PG. The ulceration can then increase in size symmetrically or asymmetrically by following the growth of its undermined edge or, alternatively, it can extend through the appearance of new peripherally placed pustules. Depth-wise, the ulcers usually do not extend into the underlying adipose tissue, but deeper lesions to the fascia are not uncommon. The ulcerations heal with atrophic, wrinkled, cigarette paper-like scars, which is a hallmark of the disease.

PG may present abruptly with the appearance of multiple, simultaneously enlarging ulcerations, or it can present less aggressively as one or two slow growing ulcers. Many variants of PG have been described including those with pustular, bullous, erosive, and vegetative morphology. For example, PG patients with inflammatory bowel disease (IBD) often have discrete pustular lesions in addition to the more classic ulcerations. Although PG typically occurs on the lower extremities, it can affect any body site. In patients who have undergone a colostomy, the peristomal region is a common location for PG to occur. PG can also present as a paraneoplastic phenomenon, most frequently seen in patients with myelodysplastic syndrome, myeloma, polycythemia vera, paraproteinemia, and leukemia. These patients have a more atypical presentation with vesiculobullous lesions and atypical sites of involvement, such as the hands. Other diseases associated with PG include autoimmune arthritis, HIV, hepatitis, systemic lupus erythematosus, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, Takayasu's arteritis, and pregnancy, among others.

CLINICAL PROBLEM ADDRESSED

The lack of clear serologic or histologic criteria to diagnose PG complicates the management of the disease. Histologic features include dermal edema, neutrophilic abscesses, and suppurative inflammation in the dermis that extends into the subcutaneous fat. Since these features can also be seen with infections, negative cultures and special stains are needed to make a diagnosis of PG. Clinically deep fungi, syphilis, insect bites, and mycobacterial infections can look similar. A broader differential would include factitious ulcerations, malignancy (metastatic or cutaneous in origin), vasculitis, parasites, venous insufficiency, and antiphospholipid antibody syndrome. In addition to skin biopsy and cultures, a typical work up often includes a colonoscopy, rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), Anti-neutrophil cytoplasmic antibodies

Table 1. *Treatments for pyoderma gangrenosum*

Treatments for Pyoderma Gangrenosum	References
Adalimumab	21
Anakinra (when associated with pyogenic arthritis, pyoderma gangrenosum and acne syndrome)	14
Azathioprine	25
Clofazamine	6
Corticosteroids	25
Cyclophosphamide	4
Cyclosporine	3
Dapsone	7
Etanercept	18
Infliximab	8
Intravenous immunoglobulin	19
Methotrexate	26
Minocycline	27
Mycophenolate mofetil	3
Sulfasalazine	28
Tacrolimus	29
Thalidomide	2

(pANCA), cANCA, complete blood count (CBC), peripheral smear, serum and urine protein electrophoresis, and a screen for antiphospholipid antibodies to assess for associated disorders.

Once a diagnosis of PG has been established, then the goal of the therapy is to reduce the aberrant inflammatory response to promote wound healing. Mild PG can be treated with topical or intralesional immunosuppressive mediations. Systemic medications that have been successful in treating severe PG include corticosteroids, sulfasalazine, dapsone, thalidomide, minocycline, clofazamine, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin (IVIG), cyclophosphamide, and biologic medications (Table 1).²⁻⁸ Unfortunately, there is no validated outcome measure for studying PG treatments, thus making it difficult to conduct clinical trials. In fact, only a single-controlled clinical trial exists, a phase II randomized, placebo-controlled study to assess the safety and efficacy of infliximab, an antitumor necrosis factor (anti-TNF) monoclonal antibody, for the treatment of PG.⁸ Given the paucity of studies, most clinical decisions are based on physician preference.

RELEVANT BASIC SCIENCE CONTEXT

Cytokines may play a role in the pathogenesis of PG. Interleukin-8 (IL-8) overexpression is present in PG ulcers, and IL-8 serum levels decrease after successful treatment of PG. In addition to IL-8, gross elevations of numerous other cytokines and proteins have been reported including IL-1 β , IL-6, IL-8, interferon gamma (IFN- γ), granulocyte colony-stimulating factor (G-CSF), TNF, matrix metalloproteinase 9 (MMP-9), MMP-10, and Elafin.⁹

Of the latter, TNF is of particular interest, as there is a strong association between PG and IBD,¹⁰ and TNF is a pro-inflammatory cytokine that is known to be associated with IBD. Thus, it is not surprising that the anti-TNF biologic medications infliximab, etanercept, and adalimumab have been successfully used to treat PG.⁸ At the molecular level, TNF is known to induce the secretion of IL-8, which is a strong chemotactic factor for neutrophils, the most predominant inflammatory cell seen in PG biopsy specimens. Keratinocytes and T cells are the two main sources of TNF in the skin. Correlating well with the possibility of an aberrant T cell response driving PG, T cell clonal expansions have been reported in patients with PG,^{11,12} and lymphocytes are present in early PG lesion.¹³ Thus, clonally expanded T cells may secrete TNF, which, in turn, drives overexpression of IL-8. The IL-8 secreted in response to the TNF is produced by a variety of cell types, including lesional dermal fibroblasts. In addition, of particular interest is the recent finding that blocking IL-1 activity with anakinra is very effective in treating PG associated with PAPA syndrome.¹⁴ PAPA syndrome is a rare autosomal dominant disease resulting from a defect in the CD2 binding protein 1 (CD2BP1) known as proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1).¹⁵ Following minor trauma patients with PAPA syndrome develop an accumulation of sterile, pyogenic, and neutrophil-rich material within their joints and skin, ultimately resulting in a destructive arthritis and PG-like skin lesions. PAPA syndrome is associated with an elevation of IL-1 β production. Anakinra, a recombinant homologue of human IL-1Ra, competitively inhibits binding of IL-1 α and IL-1 β to the IL-1 receptor type 1.¹⁶ IL-1 is a proinflammatory cytokine that is synthesized as pro-IL-1 β . Pro-IL-1 β is then converted to its biologically active form by caspase 1.¹⁷ In PAPA syndrome, binding of PSTPIP1 mutants to pyrin is believed to result in increased IL-1 β levels via increased caspase-1 activation. These findings underscore the complexity of PG and point to multiple related pathways in its pathogenesis.

EXPERIMENTAL MODEL OR MATERIAL: ADVANTAGES AND LIMITATIONS

Although there are no strong experimental models of PG, Oka and colleagues developed a model in which they grafted human skin onto severe combined immunodeficiency mice. After the grafts had been accepted, they injected them with an IL-8-expressing adenovirus. This resulted in an intense perivascular infiltration of neutrophils

that after 12h caused necrosis of the overlying epidermis. The resulting ulcers remained for weeks and looked similar to PG, both clinically and histologically.¹⁸

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

PG has been reported to respond well to many different biologic (parenterally administered protein therapeutics) medications. The anti-TNF biologics etanercept, adalimumab, and infliximab have been most commonly used. Among these, etanercept is the only one reported not to be effective in the treatment of IBD,¹⁸ which needs to be taken into consideration when designing a treatment regimen for PG. Unfortunately, there has been little consistency in the published dosing regimens of these medications. Of note, the biologic most studied in the treatment of PG is infliximab. In a phase II randomized, double-blinded, placebo-controlled study, it was found that at 2 weeks, significantly more patients in the infliximab group (5 mg/kg) showed improvement compared with placebo (46% vs. 6%, $p = 0.025$). The remission rate at 6 weeks was 21%.⁸ In addition to anti-TNF medications, IVIG has also been used to treat PG.¹⁹ A case series of patients with PG treated with IVIG revealed that seven of the ten patients experienced remission of their PG, and six of the patients could be maintained with repeat IVIG treatments.¹⁹

In addition to anti-TNF medications, other systemic immunosuppressive agents used to treat PG are listed in Table 1. Of the classic immunosuppressive agents, the most commonly used are prednisone, cyclosporine, methotrexate, and mycophenolate mofetil. We emphasize again that since PG is a chronic disease, this should be taken into consideration when designing a maintenance treatment regimen. For example, dermatologists generally tend to limit the use of cyclosporine to 1–2 years, although this is not necessarily a common practice in other specialties. Although using combinations of immunosuppressive medications to treat PG has not been highlighted in the literature, it is important to consider this option for the management of patients with refractory disease. We believe that combination therapy may be a better strategy than sequentially switching the patient from one immunosuppressive agent to another. After a patient has been well controlled for several months, remission might be maintained with a less toxic regimen. For instance, we typically

TAKE-HOME MESSAGE

Basic science advances

There is strong evidence to suggest that PG has an immunologic etiology. Elevations of a variety of cytokines have been reported in lesional skin including IL-8, IL-1 β , IL-6, IL-8, IFN- γ , G-CSF, TNF, MMP-9, MMP-10, and Elafin. Of these, IL-1 β and TNF are of particular interest, as biologic medications that target these have shown effectiveness in treating PG.

Clinical science advances

IVIG and biologic medications, such as infliximab, adalimumab, etanercept, and anakinra, are promising new treatment options for patients with PG.

Relevance to clinical care

PG ulcers form in response to minor trauma. Thus, great care should be taken to protect the skin. Surgical treatment options, such as debridement and skin grafting, should be avoided until the clinician is certain that the underlying aberrant inflammatory response has been successfully suppressed.

do not use mycophenolate mofetil for the initial management of PG, but have had good success maintaining patients on this more cost-effective medication. Drugs such as prednisone and cyclosporine may need to be slowly titrated to prevent rebound as a patient is transitioned to a less aggressive therapy, although this has not been studied to our knowledge.

INNOVATION

Over the past decade, new biologic medications have changed the landscape of treatment options for patients with immune-mediated diseases. These drugs are highly sophisticated proteins that target key components of the immune system. The structure of these medications has also become more advanced over the last few years, and there has been a marked increase in the number of targets that this class of medications can recognize. For example, infliximab is a mouse-human IgG1 chimeric anti-TNF monoclonal antibody, whereas adalimumab and golimumab are fully human anti-TNF monoclonal antibodies (IgG1). In contrast, etanercept is a TNF-specific fusion protein. Cytokines targeted by biologics include TNF, IL-1, IL-12, IL-17, and the Th1 and Th17 pathway-inducing cytokine IL-23. Other biologics target transmembrane proteins, which are important for cell adhesion and costimulation.

CAUTION, CRITICAL REMARKS, AND RECOMMENDATIONS

The opinions presented here are mainly founded on our limited understanding of the pathophysiology of PG, reported clinical studies, and our ex-

perience with less than two-dozen patients. Skin grafting and debridement are usually avoided when managing PG, as the ulcers can be induced by trauma. The exudative nature of the ulcers should be taken into consideration when choosing an appropriate wound dressing. In addition, the likelihood of bacterial colonization is high, especially in the setting of aggressive immunosuppression.

It can be extremely difficult to tease out long-term risks of starting patients on biologic medications. A large meta-analysis of patients with RA treated with infliximab or adalimumab demonstrated that patients on TNF antagonists have an increased risk of lymphoma.²⁰ In addition to a theoretical risk of lymphoma, biologics are also known to cause congestive heart failure.²¹ Reports of multiple sclerosis, peripheral neuropathy, and anti-DNA antibodies have also been published.²² However, the most concerning side effect of biologic medications is reactivation of tuberculosis.^{23,24} Patients need to be screened before the initiation of a biologic therapy and monitored closely for this infection.

FUTURE DEVELOPMENTS OF INTEREST

There is a need to develop a validated outcome measurement tool to better assess treatment outcomes in clinical studies and to compare the effectiveness of different therapies for PG. In addition, there are several novel biologic medications that

have yet to be tested in patients with PG. For example, ustekinumab blocks the common p40 subunit of IL-12 and IL-23 and, therefore, blocks the development of Th17 and Th1 cells. Given that neutrophil recruitment appears to be dependent on IL-17,²² IL-23 blockade with ustekinumab is a reasonable therapeutic strategy for patients with PG. It also remains to be seen whether anakinra will be effective in PG associated with other inflammatory conditions, for example, IBD. Certolizumab is a pegylated, humanized Fab' fragment of an anti-TNF monoclonal antibody. As is the case with other anti-TNF medications, this drug will likely be effective in treating PG. With such a plethora of possible treatment options, there are bound to be new case reports on the horizon, thus demonstrating the effectiveness of these novel medications in the treatment of PG.

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