**Effective Strategies for the Management of Pyoderma Gangrenosum: A Comprehensive Review**

Forum PATEL\(^1\), Sarah FITZMAURICE\(^1\), Christopher DUONG\(^1\), Young HE\(^1\), Jonathan FERGUS\(^1\), Siba P. RAYCHAUDHURI\(^2\), Miki SHIRAKAWA GARCIA\(^1\) and Emanuel MAVERAKIS\(^1,2\)

\(^1\)Department of Dermatology, School of Medicine, University of California, Davis, and \(^2\)Veterans Affairs Northern California Health Care System, Sacramento, USA

Pyoderma gangrenosum (PG) is an inflammatory disease characterized by painful skin ulcerations with undermined and erythematous borders. The etiology of PG is not well understood, but it is generally considered to be an aberrant immune response characterized by a dermal neutrophilic infiltrate. Given the existence of only a few PG clinical trials, treatment options are largely based upon anecdotal data and small case studies. In addition to classic immunosuppressive medications, PG has been reported to respond well to the anti-TNF agents, infliximab, etanercept, and adalimumab. Newer biologics such as ustekinumab (anti-IL-23), ixekizumab (anti-IL-17) and brodalumab (anti-IL-17R) are promising given the effect of IL-17 on neutrophil migration. However, the effectiveness of these newer agents remains to be rigorously evaluated. Multi-drug regimens have not been well described in the literature but are an excellent alternative for patients with refractory disease. Herein, we provide a comprehensive review of the pathophysiology of PG and of the different treatments available for managing PG patients, including the theoretical benefit of initiating multidrug regimens. We also provide one possible treatment algorithm for patients with refractory disease and give examples of refractory PG cases successfully treated with multidrug regimens. Key words: adalimumab; biologic; infliximab; IVIG; mycophenolate mofetil; pyoderma gangrenosum.

Accepted Nov 11, 2014; Epub ahead of print Nov 12, 2014


Emanuel Maverakis, MD, Department of Dermatology, University of California, Davis School of Medicine, 3301 C Street, Suite 1400, Sacramento, CA 95816, USA. E-mail: emaverakis@ucdavis.edu

Most commonly, a PG lesion forms at a site of minor trauma as a tender inflammatory nodule or pustule that breaks down over time to create a necrotic ulceration, a process known as pathergy. The prototypical lesions appear on the lower extremities as painful ulcerations with raised erythematous and undermined borders. The undermined border precedes the advancement of the ulcer’s edge and is an ominous sign of worsening disease. In addition to being red, the border can sometimes be purple in color. In active lesions, macular erythema can also exist peripherally to the undermined border, or in place of it in less active lesions, especially in patients partially controlled with immunosuppressive medications. Once formed, the ulceration can 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 located pustules.

The base of the ulcer is characteristically composed of excessive granulation tissue with or without neutrophilic abscesses. It usually does not extend past the underlying adipose tissue, but rare lesions involving the fascia have been reported (1). In contrast, “superficial granulomatous pyoderma” presents with superficial ulcerations that on biopsy demonstrate granulomas, plasma cells, and eosinophils (2–5).

Although PG has a predilection for the lower extremities, any body site, including the face and genitalia, can be affected. In patients who have a colostomy, the peristomal region is commonly involved (6). This is likely due to pathergy; even mild trauma can lead to large ulcerations. There are also other subtypes of PG including those with pustular, bullous, and vegetative morphologies (2, 3). Certain patient populations may be predisposed to developing a particular subtype over others and patients may have more than one subtype present simultaneously. For example, patients with PG associated with inflammatory bowel disease (IBD) often have discrete pustular lesions with or without simultaneous classic ulcerations (6, 7).

PG can also present as a paraneoplastic phenomenon, seen frequently in patients with myelodysplastic syndrome, multiple myeloma, polycythemia vera, paraproteinemia, and leukemia (8, 9). These patients can have a more atypical presentation with vesiculobullous lesions or ulcers appearing at atypical sites such as the hands (8–11).

The onset of PG can be just as variable as its clinical presentation. Some patients present with one or two slowly growing ulcers while others experience a rapid onset with the abrupt appearance of multiple rapidly enlarging ulcerations simultaneously. While waxing and waning with spontaneous resolution is possible, PG patients usually require aggressive immunosuppressive therapy to induce disease remission. The chronic nature...
of the disease usually requires long-term maintenance therapy to prevent relapses from occurring.

Although Brunsting and coworkers were incorrect in proposing an infectious etiology for PG, they did make several seminal observations (12, 13). For example, they noted the chronic nature of the disease and described the characteristic atrophic cigarette paper-like scars associated with the disease. They also reported that PG lesions do not respond well to debridement and skin grafting. In fact, they were the first to document pathergy, demonstrating that new, non-healing PG lesions often occur at skin graft donor sites. However, the most interesting observation made by this group was that PG commonly occurs in patients with severe diarrhea and inflammatory arthritis. Today, the link between PG and a variety of underlying inflammatory diseases has been firmly established.

PG affects patients of all ages but it is characteristically seen in patients between 20–55 years of age. Its incidence has been estimated to be 3–10/million based on a case series from tertiary-care facilities and cohort studies of patients with inflammatory bowel disease (14, 15). A recent population-based study by Langan et al. (16) reported a similar incidence of 6/million. Most frequently, PG has been associated with arthritis, IBD, and hematological disorders (12, 13, 16–19). IBD was found to have the highest association (20.2%), followed by rheumatoid arthritis (RA) (11.8%), and then hematological disorders (3.9%) (16–19). PG has also been associated with HIV, hepatitis, systemic lupus erythematosus, PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne), Takayasu’s arteritis, and pregnancy (20). Thus, part of the work-up for PG includes searching for underlying co-existing conditions, and the disease management should incorporate a therapy designed to treat PG as well as its associated inflammatory disorder(s) when present. Patients can be quite ill and as a group, they have a 3-fold increase in mortality compared to general population (16).

EVALUATION

Evaluating a lesion concerning for PG should start with a thorough history to assess for associated risk factors, as mentioned above, particularly for signs of IBD and internal malignancies. A focused physical exam should be performed, making particular note of the location of the lesions, characteristics of the ulcer border, and the presence of scars from previous ulcers. Multiple ulcers on the anterior lower extremities with the characteristic undermining border and surrounding erythema are nearly pathognomonic for PG. Likewise, if the disease has been long-standing, healed atrophic “cigarette paper-like” scars are also classic. The size of the undermining border can provide some insight into how rapidly the ulcer edge will evolve.

There are no clear serologic or histological criteria to diagnose PG; it is considered to be a clinical diagnosis of exclusion. The work-up often starts with a biopsy that preferentially includes part of an ulcer border and adjacent skin. Histologic features include dermal edema, neutrophilic abscesses, and suppurative inflammation in the dermis that can extend into subcutaneous fat. Within the dermis, neutrophils loosely surround perivascular lymphocytic infiltrates. Similar changes can be seen in the setting of infection. Thus, infection needs to be ruled out with tissue cultures and special stains prior to making the diagnosis of PG. Clinically, deep fungal infections, syphilis, insect bites, leishmaniasis, and mycobacterial infections can mimic PG. One must also consider factitious ulcerations, vasculitis, parasites, venous insufficiency, antiphospholipid antibody syndrome, malignancy, and other inflammatory disorders in the differential (21, 22). In addition to obtaining a skin biopsy and cultures, workup may sometimes include colonoscopy, and extensive blood and urine screening.

PATHOPHYSIOLOGY

PG is now considered to be an aberrant and possibly autoreactive immune response. It is most commonly categorized as a severe neutrophilic dermatosis that is characteristically challenging to diagnose and treat. There are several lines of evidence supporting an immunologic etiology of PG. For one, as mentioned above, patients often have a coexisting immune-mediated disease such as IBD or inflammatory arthritis (RA, ankylosing spondylitis, or other seronegative arthritis) (23–30). Second, patients treated with immune modifying medications for other conditions rarely develop PG; for example, there have been separate case reports of patients developing PG in the setting of infliximab or granulocyte-macrophage colony-stimulating factor (GMCSF) therapy (31, 32). Third, genetic diseases involving the immune system, such as leukocyte-adherence glycoprotein (LAD) deficiency, and PAPA syndrome, are associated with PG or PG-like lesions (33, 34). Finally, medications that target key components of the immune system are emerging as effective treatments for PG. Thus, there is strong correlative evidence in support of PG having an underlying immunologic mechanism; however, its exact pathophysiology is not well understood.

Oka et al. (35) developed an experimental model of PG in which they grafted human skin onto mice with severe combined immunodeficiency (SCID mice). After the grafts were accepted, they injected them with an adenovirus vector containing cDNA that encoded for human interleukin-8 (IL-8). This resulted in an intense perivascular infiltration of neutrophils, which after 12 h caused ulceration of the overlying epidermis. The ulcers were chronic, remaining for a few weeks; and
resembled PG, both clinically and histologically. A small number of other studies also exist that support the role of IL-8 in the pathogenesis of PG (35, 36). For example, IL-8 is overexpressed in PG ulcers and serum IL-8 levels fall following successful treatment of PG with systemic therapy. In addition to IL-8, elevations of IL-1β, IL-6, interferon (IFN)-γ, G-CSF, tumour necrosis factor (TNF), matrix metalloproteinase (MMP)-9, MMP-10, and Elafin have all been reported (37–40). TNF is a cytokine also well known to be associated with IBD (12, 13, 17–19) and it is not surprising that the TNF-targeting biologics infliximab, etanercept and adalimumab, have all been successfully used to treat PG (41–44). Of note, TNF is also known to induce the secretion of IL-8, which is a strong chemotactic factor for neutrophils, the predominant inflammatory cell type seen in PG biopsy specimens. Keratinocytes and T cells are the two main sources of TNF in the skin. Supporting the possibility of an aberrant T-cell response driving PG, two groups have demonstrated the presence of T-cell clonal expansions in PG patients (42, 43). Although these expansions have not been further characterized (45), they likely appear early-on in the course of disease (44). We speculate that the infiltrating T cells are directed against a processed autoantigen that has yet to be determined (46–51). In addition to T cells, a variety of other cell types, including lesional dermal fibroblasts, may also overexpress IL-8 in the setting of PG (36). As will be described later, IL-17 and IL-23 are also very critical in the pathophysiology of PG, due to their role in neutrophil migration.

In some settings IL-1 can play a major role in PG. When associated with PAPA syndrome, PG can be treated with anakinra (52). Anakinra is a recombinant homologue of human IL-1RA that competitively inhibits binding of IL-1α and IL-1β to the IL-1 receptor type 1 (53). IL-1 is a proinflammatory cytokine that initially exists as inactive pro-IL-1β within inflammatory cells. Upon appropriate signaling, pro-IL-1β is cleaved to its active form by caspase-1 (54). PAPA syndrome results from mutations in the CD2 binding protein-1 (CD2BP1) known as PSTPIP1 (55). Binding of PSTPIP1 mutants to pyrin is believed to result in increased IL-1β levels via increased caspase-1 activation (56). These pathways underscore the multifactorial and complex pathogenesis of PG. Similarly, gevokizumab is a monoclonal antibody against IL-1β and is currently being tested against PG (NCT01882504).

CLINICAL MANAGEMENT OF PYODERMA GANGRENOsum

A paucity of studies to guide clinical decision-making

The lack of validated outcome measures makes it difficult to conduct PG clinical trials. Common outcome measures such as resolution of ulcers are not ideal for assessing response to treatment because even after the pathogenic inflammation has resolved, PG lesions may take weeks or months to heal. Also, factors not associated with the pathogenic immune response (e.g. obesity, diabetes, edema, etc.) may contribute to the inability of an ulcer to heal. The relatively low incidence of disease, 3–10 patients/million, has also made conducting randomized clinical trials problematic. Currently there are only two controlled clinical trials in PG (41, 57). However, devising an appropriate treatment strategy is essential. The opinions presented here are founded mainly upon our limited knowledge of the pathophysiology of PG, case reports in the literature, our experience with approximately two-dozen PG patients, and our experience in managing other related inflammatory disorders.

Traditional monotherapy

PG is a disfiguring disease that may require aggressive therapy for optimal control. Regardless of the therapeutic agent used, the goal of therapy is the same; reduce the aberrant inflammatory response to promote wound healing while minimizing adverse drug events. Patients with mild PG have been reported to respond well to topical tacrolimus, topical sodium cromoglycate, nicotine, 5-aminosalicylic acid, intralesional triamcinolone diacetate, and intralesional cyclosporine (58–62). However, more severe presentations warrant management with systemic medications. Oral and intravenous medications that have been reported to successfully treat PG (Table SI1) include: azathioprine, corticosteroids, sulfasalazine, dapsone, thalidomide, minocycline, clofazimine, methotrexate, mycophenolate mofetil, tacrolimus, cyclosporine, intravenous immune globulin and cyclophosphamide (23, 41, 63–78). Of these, corticosteroids and cyclosporine are the best characterized. Their rapid onset of action makes them excellent choices for initial therapy. A reasonable alternative to cyclosporine is oral tacrolimus, although it has not been well studied in the setting of PG (79). Both tacrolimus and cyclosporine inhibit TCR-mediated signal transduction pathways. However, tacrolimus is 10–100 times more potent than cyclosporine in vitro (80). Other systemic immunosuppressive agents used to treat PG are listed in Table SI1. PG is a chronic disease, which should be taken into consideration when designing a maintenance treatment regimen. For example, dermatologists tend to limit the use of cyclosporine to 1–2 years, making it unsuitable for the long-term management of PG. It is however reasonable to use this fast-acting agent initially and then to transition the patient to another agent for maintenance therapy (81).

1http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2008

Acta Derm Venereol 95
Managing pyoderma gangrenosum with biologics

Over the past decade, new parenterally administered protein therapeutics have changed the landscape of treatment options for patients with immune-mediated diseases. These “biologic” medications are highly sophisticated proteins that target key components of the immune system (82). PG has been reported to respond well to many different biologic medications, most commonly the TNF blockers, etanercept, (83–88) adalimumab (89–94), and infliximab (41). In patients with coexisting IBD and PG, biologics have been reported to successfully treat both conditions simultaneously (90, 91, 94). Of the anti-TNF agents, etanercept is the only one that is ineffective in the treatment of IBD (95), which should be taken into consideration if the patient has concurrent IBD. Unfortunately, there has been very little consistency in the published biologic treatment regimens for PG. One group demonstrated successful treatment with infliximab 5 mg/kg initially followed by adalimumab 40 mg weekly (89). A case report showed complete resolution of recalcitrant PG after 4 months of treatment with 80 mg adalimumab every other week (90) and another group reported complete skin healing after 5 months of therapy with adalimumab 40 mg every other week (91). Other regimens include adalimumab 40 mg weekly or adalimumab 80 mg/week for 2 weeks followed by 40 mg/week thereafter (93, 94). 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, patients in the infliximab group (5 mg/kg every 2 weeks) had significant improvement compared to placebo (46% vs 6%, p = 0.025). The remission rate at 6 weeks was 21% (41). The relatively poor complete response rate seen in this trial underscores the treatment refractory nature of PG.

New biologics are continuously being developed and it is likely that some will prove useful in the management of PG. For example, ustekinumab blocks the common p40 subunit of IL-12 and IL-23. IL-12 is needed for the differentiation of Th1 cells and IL-23 is important for maintenance of Th17 cells. IL-17, a Th17 cytokine, is required for neutrophil migration (96). Given the predominance of neutrophils in PG lesions, IL-23 blockade with ustekinumab is a reasonable therapeutic option. Although ustekinumab has not been well characterized in PG, two case reports have demonstrated elevated expression of IL-23 in recalcitrant PG lesions. Furthermore, investigators have demonstrated the effectiveness of ustekinumab in the management of two PG patients and the medication has shown success in other neutrophilic disorders (97–99). Other biologics such as ixekizumab (anti-IL-17) and brodalumab (anti-IL-17R) will likely be effective in treating PG, given their theoretical ability to block IL-17-dependent neutrophil migration (96) but they have yet to be tested.

IL-1 antagonists (i.e. anakinra and gevokizumab) have produced a very good response in patients with PAPA syndrome but studies have not used this drug to treat PG associated with other inflammatory conditions such as IBD. They remain to be a promising treatment option and are being tested in the clinical trials setting (NCT01882504). Certolizumab is a pegylated humanized Fab’ fragment of an anti-TNF monoclonal antibody which will likely be effective in treating PG. We anticipate that there will be many new case reports in the future demonstrating the effectiveness of additional biologics in the treatment of PG.

It can be difficult to predict long-term risks of starting patients on biologic medications (82). Rare associations between infliximab and the development of hepatosplenic T-cell lymphoma have been reported (100) and other forms of lymphoma have been reported (82, 101, 102). A large meta-analysis of RA patients treated with infliximab or adalimumab also demonstrated a small increased risk of lymphoma in patients on TNF antagonists (103). Biologics have also been rarely associated with congestive heart failure, multiple sclerosis, peripheral neuropathy, and anti-DNA antibody formation (82, 104–106). Additionally, reactivation of tuberculosis remains to be one of the more concerning complications associated with anti-TNF therapy (107). Patients need to be screened prior to the initiation of a biologic therapy and monitored serially for reactivation or de novo infection while on therapy (82).

Intravenous immunoglobulin

IVIG has also been used to treat PG (108, 109). A case series reported that 7 of 10 PG patients treated with IVIG experienced remission and 6 of the patients could be maintained in remission with repeat IVIG treatments (108). Another case series reported complete clearance of 5 out of 7 PG patients treated with IVIG and significant improvement in pain was noted in all patients (110). The excellent safety profile of IVIG makes it an appealing treatment option. Adverse drug reactions to be aware of include anaphylaxis, especially in IgA-deficient individuals; aseptic meningitis; and headaches.

Surgical management

Surgery alone has not been shown to be an effective strategy for management of PG. Trauma from surgery may induce formation of new PG ulcers or cause enlargement of the existing lesion. However, we strongly recommend that patients receive traditional wound care after they have been successfully immunosuppressed. Compression, debridement, and even skin grafting can all be options for slow healing ulcers that are entirely devoid of an inflammatory border. Importantly, the persistence of an ulcer does not necessarily mean that a PG patient has failed to respond to immunosuppressive therapy. Ulcers take time to heal following successful suppres-
sion of the aberrant pathogenic immune response. Other factors such as edema, often induced by therapy with high-dose prednisone; cytotoxic immunosuppressives, which can inhibit wound healing; diabetes, induced by prednisone therapy; and heavy bacterial colonization can delay wound healing in a patient otherwise appropriately immunosuppressed. Thus, being able to distinguish a residual poorly healing, but non-inflammatory, ulcer from an active inflammatory PG ulcer is essential, as the former does not require additional immunosuppression.

Fig. 1. Example of 3 PG patients that required a multi-drug regimen in order to achieve remission. Patient 1 was initially started on etanercept with no response, and eventually required combination therapy with infliximab and low dose mycophenolate mofetil to achieve complete remission. Patient 2 was immediately started on prednisone and cyclosporine with minimal response. Adalimumab was then added, allowing prednisone and cyclosporine to be titrated off. Patient was then maintained on adalimumab for over a year before she was transitioned to maintenance therapy with mycophenolate mofetil at the lowest dose required to maintain remission (500 mg twice daily). Patient 3 was started on prednisone with minimal response and later required combinational therapy with prednisone, mycophenolate mofetil and cyclosporine. After complete response was achieved and cyclosporine was titrated off, the patient was maintained on adalimumab and mycophenolate mofetil 500 mg twice daily. All 3 cases are from the University of California, Davis Rheumatology/Dermatology clinic.
Combination therapy

Fig. 1 shows our personal clinical experience with 3 patients with refractory PG lesions successfully treated with multidrug regimens. Combination therapy for PG has not been highlighted in the literature, but it is important to consider this option for the management of patients with refractory disease. Due to the lack of controlled trials, we recommend using well-studied immunosuppressive drug combinations that are known to be effective in other immune-mediated diseases. For example, methotrexate is commonly used in conjunction with infliximab, but never with mycophenolate mofetil. The combination of cyclosporine (or tacrolimus), mycophenolate mofetil, and prednisone is often used to treat hematopoietic transplant patients with graft-versus-host disease. Ultimately, a multidrug regimen may be a better strategy than sequentially switching a patient from one immunosuppressive agent to another. Ideally, synergistic drug combinations would allow for better long-term management with fewer adverse drug events. For example, concomitant administration of cyclosporine and rapamycin at subtherapeutic doses reduces the drugs’ respective toxicities but not their effectiveness (111). One group reported complete resolution of PG ulcers with a regimen of intravenous cyclophosphamide pulse therapy (1,000 mg/month), cyclosporine (100 mg/day), and prednisone (30 mg daily tapered to 20 mg daily after 2 months) (112). Another group reported complete response with a combination of cyclosporine (10 mg/kg), mycophenolate mofetil (2 g daily), and negative pressure dressings (113). Yet another group successfully treated an infliximab and azathioprine-resistant PG patient with a combination of adalimumab (80 mg SQ weekly), cyclosporine (3 mg/kg), prednisone (20 mg daily), and sulfasalazine (2 g daily) (90).

Another therapeutic approach is to treat patients with combination therapy initially and then attempt to maintain remission with a less toxic regimen after the patient has been well-controlled for several months. For example, the slow onset of mycophenolate mofetil makes it a poor choice for the initial management of PG, but it may be an excellent alternative for maintenance therapy. Drugs such as prednisone and cyclosporine have fast onsets and are therefore excellent choices for a patient’s initial management. During the transition the initial medications may need to be titrated down slowly to prevent rebound as a patient is transitioned to a different drug for maintenance therapy.

CONCLUSION

Fig. S1 depicts one possible algorithm for the management of patients with PG, based on current medical knowledge (Table S1) and our personal clinical experience (see Fig. 1). Given the adverse drug reactions associated with classical immunosuppressive medications and the severe morbidity associated with PG, biologics are an excellent therapeutic option for PG patients.

ACKNOWLEDGMENTS

EM was supported by early career awards from the Burroughs Wellcome Fund and the Howard Hughes Medical Institute. Funding sources: This study was supported by career awards from the Howard Hughes Medical Institute and the Burroughs Wellcome Fund, EM.

The authors declare no conflicts of interest.

REFERENCES

Vahlquist A, Håkansson LD, Rönnblom L, Karawajczyk


Acta Derm Venereol 95