Pyoderma gangrenosum (PG) was first described by Brunsting et al. in 1930 as an idiopathic, ulcerative, inflammatory dermatologic condition that occurs in approximately 1% to 5% of patients with inflammatory bowel disease (IBD). This inflammatory skin disorder is presumably caused by an autoimmune mechanism and the diagnosis is one of exclusion. PG is not a common condition but it is thought to account for approximately 50% of chronic parastomal ulcers. Refractory parastomal PG (PPG) occurs in patients with inactive disease or after bowel resection. Multiple medical treatments, ranging from topical agents for mild disease to systemic immunosuppressive therapy for severe disease, have been used with varying rates of success. Using topical tacrolimus, an immunosuppressant that inhibits T-lymphocyte proliferation, and meticulous stoma care can result in successful treatment.

Two women (ages 59 and 62 years) with a history of ulcerative colitis and colon resection presented with parastomal ulcers consistent with PPG. The 59-year patient presented with a painful 2 cm x 2 cm parastomal ulcer that improved following daily application of topical tacrolimus 0.1%. The 62-year old woman first was prescribed daily appliance changes and application of topical triamcinolone 0.5% to her 3-cm ulcer. The ulcer increased in size and treatment was changed to daily application of tacrolimus 0.1%. After 2 months and a reduction in ulcer size and severity, the dosage was changed to daily application of tacrolimus 0.03%. Both patients reported resolution of pain and itching, the most common symptoms of PPG, and no adverse effects were observed. The encouraging results observed in these two cases confirm that tacrolimus helps resolve PPG lesions even at concentrations previously thought to be ineffective. Additional studies to help clinicians optimize care of these painful lesions are needed.

Key Words: colostomy, pyoderma gangrenosum, tacrolimus, parastomal ulcer

Potential Conflicts of Interest: The authors have nothing to disclose.
chronic parastomal ulcers. Frequently misdiagnosed, the actual incidence of this disorder is difficult to confirm.

**PPG Management**

PPG is particularly difficult to manage, especially in refractory cases. The successful treatment of PPG involves healing of the ulcer and control of ostomy function with meticulous stoma management. The treatment regimen is based on individual response and can be local, systemic, or in some refractory cases, surgical. Local treatment includes wound care, topical agents, and local injection of medications. Local wound care including debridement, curettage, and deroofing the ulcer complex is often insufficient. Unsuccessful treatment can result in stoma relocation. Use of topical agents including antibiotics, corticosteroids, Desitin ointment (Pfizer, Inc., New York, NY), and 0.5% nicotine cream has been described and provides variable efficacy. Systemic therapy such as dapsone, prednisone, cyclosporine, mycophenolate mofetil, and intra-venous infliximab remain the mainstay of treatment. In refractory cases or in patients with inactive or resected disease, topical tacrolimus can be beneficial.

Tacrolimus (FK506) is a potent member of the macrolide family of immunosuppressive antibiotics. It acts by blocking the IL-2 transcription, thereby inhibiting T-lymphocyte proliferation and activation. Systemic therapy with tacrolimus has been shown to be effective in a variety of lymphocyte-driven inflammatory dermatoses, although adverse effects of the systemic treatment such as hypertension, neurotoxicity, and nephrotoxicity have been shown. In order to circumvent the adverse effects of systemic therapy, topical treatment strategies have been evaluated in many case studies. Studies using 0.3% tacrolimus ointment report rare adverse reactions, such as burning, pruritus, flu-like symptoms, allergic reactions, and skin erythema. Manufacturer contraindications for the use of tacrolimus include a known allergy to tacrolimus or one of the components of the preparation. Tacrolimus should not be used in the pediatric population or on any lesion of infectious origin.

Applied topically, tacrolimus penetrates skin effectively and has been used in a wide array of inflammatory dermatoses, such as graft versus host disease, vitiligo, contact dermatitis, and alopecia. Results of case series indicate that topical tacrolimus has been one of the more effective local agents in the treatment of PPG. Schuppe et al reported a case of a 32-year-old woman who developed a rapidly growing ulcer on her right calf. On admission, the ulcer had a 10-cm diameter and showed typical features of PG. Although ulcer enlargement ceased with standard treatment with oral prednisolone (100 mg daily), healing was achieved after 2 weeks of daily topical applications of tacrolimus (0.5% solution). The authors used topical tacrolimus alone under a hydrocolloidal wound dressing. The skin lesion completely resolved at 12 weeks after discontinuation of the steroids. No adverse effect other than a burning sensation was noted. Reich et al described two cases where patients with PG were treated successfully with tacrolimus ointment alone and in combination with systemic cyclosporine. The first case involved a 48-year-old man with recurrent ulcerative lesions. Although previous lesions had responded to traditional treatment comprising systemic prednisolone and low-dose cyclosporine, the recurrent lesions failed to respond. When the patient developed a 2-cm lesion over the clavicle, the authors started monotherapy consisting of twice-daily application of tacrolimus ointment (0.1%). The lesion healed in 3 weeks. The second patient, a 27-year-old woman with a 4-year history of ulcerative colitis, presented with several lesions ranging from 5 cm to 10 cm in diameter. This patient was treated with systemic cyclosporine at 5 mg/kg/day, which was tapered, and 0.1% tacrolimus ointment applied once daily with a hydrocolloid dressing for 3 weeks. The authors concluded that the addition of tacrolimus accelerated lesion healing.

To compare treatment with topical tacrolimus and clostebasol propionate, Lyons et al followed 30 patients with PPG. Topical tacrolimus 0.3% in Orabase (ConvaTec Ltd., Uxbridge, Middlesex, UK) was given to six patients who had failed to respond to topical corticosteroids, systemic corticosteroids, or cyclosporine. In five of the six patients, PPG healed within 6 weeks following application and the last patient was controlled with systemic tacrolimus. The authors concluded that tacrolimus is an effective treatment in ulcers >2 cm. Furthermore, based on the results observed in 11 patients, they found that treatment with tacrolimus in concentrations less than 0.3% was ineffective.

This article presents two cases in which topical tacrolimus 0.1% was used successfully in the treatment of PPG.

**Case Report 1**

Ms. A, a 59-year-old woman with a medical history unremarkable other than for pan-ulcerative colitis, underwent a colonoscopy that revealed multiple polyps. The majority of the biopsies performed revealed chronic colitis without dys-
plasia. One 4 cm x 5 cm polyp in the region of the sigmoid and descending colon was described as a dysplasia-associated lesion or mass (DALM). A total proctocolectomy with end ileostomy was performed. Postoperatively, Ms. A recovered well and did not require any further post-resection medical treatment but 11 months later, Ms. A noticed two small ulcers on the right side of the stoma. These developed into an irregular shaped 2 cm x 2 cm painful ulcer with raised edges and a violet hue in one area of the wound border (see Figure 1). The lesion was clinically identified as PPG.

Ms. A was prescribed daily appliance changes and application of topical tacrolimus 0.1 % ointment. No special parastomal skin care preparations were used and the ointment was placed directly under the adhesive pouch. Six weeks later, the lesion had markedly improved with new skin forming on the lower edge of the parastomal ulcer and a healthy stoma (see Figure 2). Ms. A’s treatment was altered to tacrolimus ointment 0.03% ointment and every-other-day appliance changes. The dosage was lowered and appliance changes were performed in this frequency to ensure use of the minimal concentration tacrolimus and to reduce parastomal trauma from frequent appliance changes. Two months later, the PPG had improved substantially and itching and pain had resolved (see Figure 3). Ms. A experienced a brief resurgence of her symptoms and skin changes with an unintended hiatus in her therapy. She was restarted on topical tacrolimus 0.1% ointment and after a few weeks of therapy, her symptoms resolved.

Case Report 2
Ms. B, a 62-year-old woman with a history of chronic ulcerative colitis who underwent a total proctocolectomy and ileostomy due to pan-colitis, DALM, and poor sphincter function presented with pain, bleeding, and ulceration around her right lower quadrant ileostomy after trauma to her stoma. Her medical history was otherwise unremarkable. Examination revealed a healthy ileostomy with a tender, 1 cm x 1 cm ulcerated skin lesion on the right side of the stoma with raised edges clinically consistent with PG (an infectious etiology was not found). Therapy with topical triamcinolone 0.5% and daily appliance changes was initiated. However, this treatment was unsuccessful and the ulcerative process progressed. After 1 month, Ms. B’s lesion had enlarged to a 3-cm ulceration with excoriation of the left lateral and left inferior parastomal skin. Daily appliance changes and topical application of tacrolimus 0.1% ointment were prescribed. Over a few weeks, rapid improvement was noted and the tacrolimus was decreased to 0.03% concentration after 2 months along with careful monitoring by the enterostomal therapist and daily appliance changes. The ulcer and areas of excoriation were completely healed 4 months after topical tacrolimus therapy was initiated.

Discussion
In both cases of patients presenting with PPG, topical tacrolimus 0.1% was effective, confirming previous reports about the usefulness of topical tacrolimus in the management of refractory PPG in ulcerative colitis and Crohn’s disease. In both cases, after improvement of the lesions with use of topical tacrolimus 0.1%, tacrolimus 0.03% was able to be used until complete resolution. No side effects such as a burning sensation, erythema, or pruritus were noted.
The time between stoma creation and onset of the lesion is variable. Development of PPG is believed to be related to underlying IBD; therefore, control of the underlying disease should result in lesion improvement. As mentioned previously, the successful treatment of PPG involves not only ulcer healing but also successful stoma management. For this reason, PPG treatment can be an immediate and ongoing challenge as lesion healing may result in irregular scarring, which can compromise proper fitting of the appliance and lead to leakage.

The results of several observational studies have shown that topical tacrolimus may cause hyper-granulation tissue to develop in healing ulcers, possibly through a mechanism involving granulocyte-macrophage colony stimulating factor (GM-CSF). GM-CSF is a cytokine that promotes white blood cell production and granulation tissue formation. The presence of hypergranulation tissue also affects stoma appliance adherence. Lyons et al. addressed these concerns by adding topical corticosteroids in the form of an impregnated tape to the treatment with topical tacrolimus to help protect the ulcer from trauma by the tape and limit over-granulation with the corticosteroid. In Lyons’ study, tacrolimus 0.3% in carmellose sodium paste was used and it was concluded that concentrations <0.3% were not effective. Baig et al. described two cases of PPG in Crohn’s disease that were successfully treated with 0.01% topical tacrolimus; both patients in the current case study responded well to a concentration of 0.1%. The reasons for the efficacy of different doses are unknown. Possible explanations may be related to the extent and severity of disease.

In all cases, successful treatment relies on diligent ostomy care. No prognostic indicators of successful treatment have been noted other than clinical response to therapy. Similarly, results of recurrent application, required by one of the current study patients, has not been widely reported.

Obstacles to successful treatment of PPG, such as stoma appliance adherence, can be overcome without much difficulty.

Conclusion

Two case reports concur with the available literature regarding successful treatment of PPG with topical tacrolimus. Although PPG is rare and large randomized trials are unavailable, topical tacrolimus used in conjunction with good stoma care can be a useful and successful treatment strategy for refractory PPG.

References

5. McCarthy WC, Robertson DB, McKeown PP, et al. Pyoderma gangrene-