Review

A Comprehensive Review of Local Pharmacologic Therapy for Pyoderma Gangrenosum

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This literature review assesses all available local therapies in order to summarize the use and reported efficaciousness of the broad range of local treatments available for PG.

Abstract

Pyoderma gangrenosum (PG) is a rare, ulcerative inflammatory skin disease that most commonly occurs in patients with inflammatory bowel disease, rheumatologic diseases, or hematologic diseases. Successful treatment of PG often requires immunosuppression and appropriate wound care. Systemic corticosteroids and cyclosporine are the first-line treatments for PG. However, chronic use of these systemic agents places patients at risk for developing significant side effects, including hyperglycemia, osteoporosis, hypertension, and weight gain. Furthermore, when treating small or superficial PG ulcers, the use of local agents as monotherapies or adjuvant treatments can be ideal to control inflammation and promote healing without placing the patient at risk for many severe side effects that can be seen with long-term use of systemic agents. This literature review assesses all available local therapies in order to summarize the use and reported efficaciousness of the broad range of local treatments available for PG.

Pyoderma Gangrenosum: An Uncommon Case Report and Review of the Literature

Outcomes in Fournier's Gangrene Using Skin and Soft Tissue Sparing Flap Preservation Surgery for Wound Closure: An Alternative Approach to Wide Radical Debridement

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Introduction

Pyoderma gangrenosum (PG) presents as a painful ulcer with violaceous edges and extensive undermining of the border.[1] It is an autoinflammatory skin disorder and lacks a diagnostic gold standard.[2-4] Many cases of PG are associated with diseases that cause chronic inflammation, such as inflammatory bowel disease (IBD), rheumatoid arthritis, or hematologic malignancy.[2,4] The clinical course is unpredictable, and successful treatment requires reducing inflammation and optimizing wound care. The use of systemic steroids in treating PG was first described in the 1950s and is currently the first-line treatment.[5] However, since the prolonged use of systemic steroids can lead to significant side effects, the use of topical and intralesional treatments have been investigated since the 1960s.[6,7] Localized use of immunosuppressants and immunomodulators has been reported to be beneficial in the treatment of PG. Given the critical role of local therapies in PG treatment, the authors aim to review the mechanisms of action and supporting evidence for the currently available topical medications. A summary of treatments is compiled in the **Table 1A** and **Table 1B.**

Methods

Two investigators conducted a search of English language publications using MEDLINE, PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and EBSCO databases from inception until November 2017. The search used a combination of key words and controlled vocabulary for the concepts *pyoderma gangrenosum*, *topical treatments*, *injectable treatments*, *corticosteroids*, and *immunomodulatory*, which were adapted to each database. Citations of retrieved articles were searched to extract publications not identified in the database search.

Results

Topical immunosuppressant drugs

Corticosteroids (2 studies, 50 patients). By inhibiting proinflammatory mediators, such as interleukin-1, leukotrienes, and prostaglandins, topical and intralesional corticosteroids can be a favorable alternative to systemic steroids.[8] Systemic steroids carry the risk of serious adverse effects (eg, osteopenia, avascular necrosis of the hip, glucose insensitivity, and cushingoid symptoms). In fact, the extensive profile of adverse effects are a known barrier to the use of systemic steroids among patients.[9]

Topical corticosteroids of varying strengths have been proven to be effective in the treatment of PG. Class I corticosteroids are frequently utilized, but others also have been used for treatment.[9] Clobetasol propionate commonly is used as a monotherapy to treat PG.[9,10] In 1 case report, clobetasol propionate 0.05% cream applied twice daily to the ulcer bed demonstrated complete healing of PG within 9 weeks.[9] In another prospective cohort study,[10] 49 patients were treated solely with topical clobetasol propionate 0.05% (cream or ointment), resulting in an average healing time of 18 weeks.[10]

Although Class I corticosteroids are typically used, some benefit has been shown with weaker classes, including methylprednisolone cream (Class VII corticosteroid) used as adjuvant therapy

with silver sulfadiazine.[11] However, topical corticosteroids are not without risk, as they are associated with adverse effects such as skin atrophy, telangiectasias, stria, purpura, tachyphylaxis, steroid acne, and ulceration.[12]

Calcineurin inhibitors (6 studies, 19 total patients). Calcineurin inhibitors include cyclosporine, tacrolimus, and pimecrolimus. Through the inhibition of T-cell activation and proliferation, cyclosporine has been shown to be an efficacious topical treatment for PG when used as a monotherapy or in combination with other topical medications. Azizan et al[13] used topical cyclosporine as a monotherapy and found 3 out of 4 PG ulcers achieved complete healing after 4 months. Bertoló et al[14] used topical cyclosporine in combination with topical clobetasol and gentamicin; this combination ointment applied twice daily resulted in resolution of PG ulcers in just 3 weeks.

Marzano et al[15] also have shown tacrolimus can be an effective topical monotherapy. Five patients with localized PG, defined as 1 to 3 lesions totaling < 5% of total body surface area, were treated with topical tacrolimus.[15] Healing in all 5 patients was achieved in an average of 6 weeks.[15] The efficacy and safety of topical tacrolimus as an agent for treating PG has been described by the same author in a study proposing a therapeutic algorithm for PG.[16] Furthermore, tacrolimus has been shown to be effective when used as an adjuvant therapy to oral corticosteroids, where in separate case reports, ulcers demonstrated rapid and complete healing at 3 and 8 months, respectively.[17,18] In another prospective cohort study of 10 patients treated with only topical tacrolimus, patients experienced an average ulcer healing time of 23 weeks.[19] Dosages of topical tacrolimus vary; however, tacrolimus ointment (0.03% and 0.1%) and tacrolimus solution (0.5%) have been demonstrated to be effective in treating PG.[17-19]

Pimecrolimus is another calcineurin inhibitor that has been shown to be efficacious when used as an adjuvant treatment with systemic steroids. In a patient with deep PG ulcers on the limbs, pimecrolimus was applied twice daily, contributing to healing within 3 months.[20]

The most common adverse effect of topical calcineurin inhibitors is a burning sensation upon application, which can be reduced by refrigerating the medication prior to application.[20-22] Major concerns are typically due to systemic absorption. Systemic absorption is proportional to the size of the wound; a larger wound has a higher likelihood of absorption. To avoid adverse effects, serum drug level concentrations should be monitored while a patient uses a topical calcineurin inhibitor.[21] When comparing calcineurin inhibitors, topical pimecrolimus has a lower bioavailability than tacrolimus, making it less likely to be absorbed systemically through the skin, thus reducing the risk for systemic adverse effects.[21]

Intralesional immunosuppressants

Intralesional corticosteroids (3 studies, 3 patients). The mechanism of action and adverse effects of intralesional corticosteroids are identical to that of topical steroids. Moschella[7] was the first to demonstrate that intralesional injections of corticosteroids are a viable alternative for the treatment of PG. Triamcinolone diacetate (6 mg/mL) was injected every 2 days for 14 days in a patient with a PG ulcer of the lower extremity, and complete resolution of the wound was noted at 3 weeks.[7] Another report[6] described the use of intralesional triamcinolone as an adjuvant 1-time dose of 2.5 mL (40 mg/mL) in a patient receiving systemic methylprednisolone, leading to complete wound healing in 8 weeks.

In addition to triamcinolone injections, an intralesional dexamethasone solution as an adjuvant therapy was effective in a 51-year-old man with previous history of PG who was admitted to the hospital due to a PG ulcer on the central chest.[23] Upon admission, his maintenance oral minocycline dose was increased and administered with systemic prednisone and dapsone. Negative pressure wound therapy also was employed. After 60 days of treatment, there was no change in the size of the ulcer. Then, it was decided to pursue intralesional treatment with dexamethasone solution. A solution of heparin and saline initially was used to flush the ulcer site for the first week, then 20 mg of dexamethasone was added to the solution daily for an additional 30 days.[23] There was a dramatic decrease in ulcer size 30 days after therapy initiation, and full healing was noted on a follow-up visit at 17 months.[23]

Intralesional methotrexate (1 study, 1 patient). Methotrexate is a folate analog that inhibits dihydrofolate reductase and increases levels of adenosine, which has been demonstrated to have anti-inflammatory effects.[24] The anti-inflammatory nature of methotrexate is a potential explanation for its noted effectiveness in the treatment of PG. Del Puerto et al[25] demonstrated the use of intralesional methotrexate as beneficial in treating a patient with chronic PG ulcers on the bilateral calves. The PG proved to be recalcitrant to a combination of systemic prednisone and methotrexate.[25] The route of methotrexate was changed from oral to an intralesional injection (0.5 mL of 50 mg/mL solution), which was given weekly for 7 weeks, and the patient had a 90% improvement in the size of the ulcer.[25] The most common topical side effects are burning and local irritation. Some systemic adverse effects of intralesional methotrexate, such as gastrointestinal complaints, may occur. Chronic use of methotrexate is associated with hepatotoxicity.[26]

Immunomodulator drugs

Cromolyn sodium (4 studies, 8 patients) Cromolyn sodium blocks calcium channels within the mast cells, which stabilizes the mast cell and prevents degranulation. It is not exactly clear how this mechanism relates to PG pathogenesis, but there is a study that demonstrates cromolyn sodium inhibiting chemoattractant peptides for neutrophils at lower concentrations.[27]

There have been several reports[27-29] demonstrating the effectiveness of using a topical cromolyn solution in treating PG. Cromolyn sodium has demonstrated success with varying concentrations (1%–4%), application frequency, and as an adjuvant or monotherapy. Tamir et al[27] reported 5 patients with PG who were treated with both systemic corticosteroids and topical 1% sodium cromoglycate. Upon treatment initiation, all patients had an immediate decrease in pain. In addition, granulation tissue formed in the wound bed within 3 to 7 days, and full resolution was noted within 5 to 8 weeks.[27] de Cock et al[28] used a 4% disodium cromoglycate solution as a monotherapy on a PG ulcer of the lower extremities. The patient was treated 4 times daily, and within 3 days, reepithelialization occurred, with a majority of the ulcer healed by 16 days. Additional studies performed by Smith et al[29] and Safoui et al[30] demonstrated successful treatment of PG with 2% cromolyn sodium solutions. In those studies,[29,30] response to treatment was seen as early as 4 days, and near-complete resolution was seen in 10 to 18 days. Common adverse effects with topical application of cromolyn solutions includes irritation, redness, and burning at the site of application.[31]

Benzoyl peroxide ([BPO] 1 study, 1 patient). The exact mechanism of how BPO works to aid with local immunomodulation and healing is unknown. It is postulated that as an oxidizing agent, BPO can increase tissue oxygen content and stimulate epithelial cell growth.[32] Topical BPO has proven to be an effective monotherapy for PG. Nguyen and Weiner[32] treated a PG ulcer with 20% BPO solution soaked in gauze twice daily with barrier cream to minimize any direct skin irritation caused

by BPO. Almost complete reepithelialization was observed at 4 weeks.[32] Adverse effects of BPO are minimal and include risk of epidermal irritation and contact dermatitis.[32]

Aminosalicylic acid (1 study, 1 patient). Systemic aminosalicylic acid (ASA) routinely is used for the treatment of IBD because of its ability to decrease the production of prostaglandins and leukotrienes.[33] In treatment of PG, ASA inhibits leukocyte motility and cytotoxicity, which decreases tissue destruction.[33] A patient with Crohn's disease and lower extremity PG was treated with prednisone and topical 10% 5-ASA cream daily, and complete healing was attained at 5 weeks.[33] No side effects were noted with the use of topical ASA.[33]

Phenytoin (1 study, 6 patients). In the past, phenytoin was used for war-related wounds and ulcers refractory to conventional treamtent.[34] Phenytoin stimulates fibroblast proliferation, enhancing the formation of granulation tissue and decreasing collagenase activity. This decreases bacterial wound contamination and wound exudate.[34,35] Fonseka et al[35] reported on 6 patients with PG ulcers that were treated with a topical 2% phenytoin solution once daily. By the end of week 4, 4 of 6 patients had demonstrated complete healing and the remaining 2 demonstrated significant improvement.[35] The most common adverse effect of phenytoin is a burning sensation upon topical application.[35]

Nicotine (2 studies, 2 patients). In 2 different cases, Patel et al[36] demonstrated nicotine, an antineutrophilic agent, is an effective treatment of neutrophil-mediated PG. One patient had a new PG ulcer of the foot, while the other had 3 recurrent PG ulcers.[36] The report used 0.5% nicotine cream applied daily.[36] The cream was applied to the wound bed and used in conjunction with systemic steroids. The combination resulted in complete healing within 4 to 8 weeks.[36] As nicotine stimulates the autonomic nervous system, monitoring tachycardia and hypertension are of heightened concern for patients treated with this drug.[36]

Becaplermin (1 study, 1 patient). Becaplermin is a topical version of platelet-derived growth factor (PDGF) that has been used to treat PG. The mechanism of action is to promote the recruitment and proliferation of cells involved in wound repair.[37] A patient with a PG ulcer of the hand was treated with systemic corticosteroids and topical 0.01% PDGF.[37] The topical treatment was applied daily with an occlusive dressing and barrier cream was applied around the wound edges, resulting in complete resolution of the ulcer after 9 weeks.[37] The most frequently reported adverse reactions to becaplermin are pain, skin irritation, wound infection, cellulitis, and osteomyelitis.[38]

Timolol (1 study, 1 patient). Beta2_adrenergic activation of keratinocytes slows cell migration and impairs wound healing.[39] Thus, beta2-antagonists such as timolol can help promote wound healing.[39] Timolol had been used successfully for treatment of PG in 1 case report.[39] In this patient, the ulcer initially was treated using intralesional steroid injections, topical dapsone, and systemic corticosteroids. The initial treatment of the ulcer was partially effective. After 1 month, daily application of topical timolol maleate 0.5% gel applied to the wound edges was added to the regimen. At day 60, the PG ulcer had remained unchanged. At this point, all other treatments were stopped except for the topical timolol, and topical collagenase was added to the treatment regimen. Over the next 30 days, the wound bed demonstrated decreased necrotic tissue with improving granulation tissue.[39] After another month, the wound bed had completely healed.[39]

Although no side effects were noted in the case report, concerns for systemic effect are present. As noted in the case report[39] in which topical timolol is used, decreased heart rate and blood pressure can occur.[40]

Other local agents

Nitrogen mustard (1 study, 1 patient). Topical nitrogen mustard is not commonly used for treatment of PG, but there is a case described in the medical literature reporting its efficacy.[41] The exact mechanism of action is not clearly understood, but it is a known cytotoxic agent.

A patient presented with recurrent PG associated with IgA monoclonal gammopathy resistant to steroids and plasmapheresis.[42] The patient was treated with topical nitrogen mustard due to its past documented use in treating "ulcerative" cutaneous Langerhans cell histiocytosis.[42] A 20% nitrogen mustard solution was applied to the wound bed daily and covered with an occlusive dressing, and complete healing was obtained in 3 months.[42] Due to the cytotoxic nature of nitrogen mustard, the major adverse effect experienced with nitrogen mustard is contact dermatitis.[41]

Cannabis (1 study, 3 patients). Cannabis is thought to control pain through action on the central nervous system. The exact mechanism of action of topical cannabinoids currently is not fully understood. One theory is that activation of peripheral cannabinoid receptors hyperpolarizes pain neurons, thus requiring increased stimulus to fire.[43] Although still under investigation, a recent study[44] conducted with medical cannabis oil demonstrated a significant ability to decrease the pain in the management of 3 patients with PG. Varying mixtures of tetrahydrocannabinol and cannabidiol oil were applied directly to the wound bed at least once daily for pain.[44] This decreased the need for opiates and nonsteroidal pain medication in all patients in the study.[44] Notably, the use of cannabis in the study was targeted at pain control, and closure of the wound was not described.[44] One concern was the potential for systemic absorption of the drug, which can lead to commonly reported adverse effects such as motor dysfunction and hypoactivity.[43]

Failure therapies (2 studies, 3 patients). Some topical therapies (eg, collagenase and maggots) have not been proven to be efficacious in the treatment of PG.[45,46] Duncan and Worswick[45] reported collagenase (used for enzymatic debridement) was ineffective in treating a patient with recurrent PG. After initial topical treatment with collagenase, the ulcer continued to deteriorate, accompanied by worsening blood loss, and the patient ultimately had to be admitted to the hospital.[45] However, it is important to note that this patient was lost to follow-up and was initially started on collagenase by a wound care provider who was familiar with the previous diagnosis of PG.[45] The patient also was not receiving any systemic immunosuppressive medications at the time of initial application.[45]

The use of maggots has been shown to be efficacious in the treatment of necrotic wounds.[46] However, in a study performed by Renner et al,[46] maggot therapy was not beneficial in treating PG in 2 patients. When maggot therapy was applied and checked 24 to 72 hours later, all maggots had died, and the PG ulcers had not improved.[46] The authors[46] hypothesized 2 theories of why the maggots died: first, cytokines, metalloproteinases, and reactive oxygen species produced by the neutrophils may have been toxic to the maggots; and second, the use of immunosuppressant drugs and their interaction with the maggots, as immunosuppressant medications can be toxic to mosquito larvae, blowfly larvae, and other insect larvae. Thus, it is likely that the toxicity of immunosuppressant drugs to maggots inhibited their potential biologic effect in wound healing.[46]

Limitations

The limitations of this review include the status of PG as a diagnosis of exclusion without reliable biological or laboratory markers for definitive diagnosis. There continues to be a need for development, reliability testing, and validation of a severity rating system for PG so that outcomes can be adjusted for PG severity or risk factors such as wound size, degree of inflammation, and pain. Due to the use of case reports in this review, there also is a lack of standardization when comparing treatments and patient response.

Conclusions

Currently, there are numerous treatments for PG, the most common of which are systemic immunosuppressants and immunomodulators. However, their adverse effect profiles and the possible inadequate clinical response can limit their use in some patients with PG, at which point local therapies become crucial in the management of PG. Local treatments commonly target inflammation to treat small or superficial ulcers. They also can be used as adjuvant therapy when systemic medications are providing an insufficient response as monotherapies or are being tapered down. Additional research is needed to determine which patients would most benefit from either local monotherapy or adjuvant systemic and local therapy. It is unclear what kind of patients with PG respond best to topical management, though these topical medications are important therapeutic options at the disposal of clinicians. Understanding their mechanism of action and mode of application are important features when clinicians are considering topical medications for treatment of PG lesions.

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