

# A Novel Therapy for the Treatment of Pyoderma Gangrenosum

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## SUMMARY

Pyoderma gangrenosum (PG) is an uncommon, chronic, painful, ulcerative skin disease of unknown origin, often associated with systemic diseases including inflammatory bowel disease, rheumatoid arthritis, monoclonal gammopathy, hepatitis and myeloproliferative disorders. The mainstay of therapy for PG has been high-dose corticosteroids but not all patients have a favourable outcome. Other systemic agents have also been used such as cyclosporine, azathioprine, cyclophosphamide and tacrolimus. However, all these systemic therapies can be complicated by serious side effects. In this paper, we report a series of four patients with pyoderma gangrenosum treated successfully with topical cyclosporine. No side-effects were observed in any of the patients and there was minimal systemic absorption of the topical cyclosporine.

## INTRODUCTION

Pyoderma gangrenosum (PG) was first described by Brunsting, Goeckerman and O' Leary in 1930 on five patients who had painful, enlarging necrotic ulcer with bluish undermined edges surrounded by an advancing zone of erythema<sup>1</sup>. Four of them had ulcerative colitis. PG is an idiopathic, painful, chronic inflammatory and ulcerative skin disease characterized by variable clinical presentations and outcome. The aetiology of PG is unknown but has been reported to be associated with systemic diseases including inflammatory bowel disease, rheumatoid arthritis, monoclonal gammopathies, hepatitis and myeloproliferative disorders. Effective management of PG requires a multidisciplinary approach and is dependent on the diagnosis and treatment of any underlying disorder<sup>3,5</sup>. As its incidence is low, there has been no controlled trial on the management of this rare skin condition. While, systemic steroids remains the mainstay of therapy, other immunosuppressive agents have been proven to be beneficial for example systemic cyclosporine and tacrolimus<sup>3,4,5,6,7</sup>. However, prolonged therapy with systemic agents is associated with significant side effects. Therefore, there is certainly a need for a quest of an effective and safe topical agent for the treatment of PG. The purpose of this study was to determine the effectiveness and safety profile of topical cyclosporine in the treatment of PG.

## MATERIALS AND METHODS

This is a prospective study on four patients diagnosed with pyoderma gangrenosum, with a wide range of underlying

diseases and occurring at various body sites. These ulcers were refractory to conventional therapy and were treated with topical cyclosporine. All patients underwent a full evaluation including history, physical examination and laboratory investigations which included a full blood count, erythrocyte sedimentation rate, renal profile, liver function test, autoimmune panel of autoantibodies, syphilis serology, gastrointestinal evaluation including endoscopy and colonoscopy when indicated by history or physical examination. For genital PG, a complete sexually transmitted screen was also carried out. All patients had a skin biopsy and tissues were sent for bacterial, fungal and mycobacterium cultures.

The cyclosporine used was the intravenous preparation for systemic administration (1 ampoule of 50mg/ml). 1 ampoule of 50mg/ml was diluted (1:1) with distilled water. This mixture was poured onto a piece of lint which was then placed over the ulcer that has been cleaned accordingly. An occlusive transparent dressing (e.g. Tegaderm) was used to cover the ulcer. Topical cyclosporine was applied initially once daily for all patients. Subsequently, according to patients' response, treatment was carried out every other day. The patients' ulcer was evaluated weekly with measurements, ulcer tracing and photography. Patients assessment of pain was also recorded weekly using the Visual Analogue Scale. (0-10). A complete blood count, biochemistry panel and serum trough level of cyclosporine were also repeated every two weeks during treatment.

## RESULTS

The demographics of the study patients is illustrated in Table I. Three subjects had an associated underlying condition which is rheumatoid arthritis, Behcets disease and cutaneous polyarteritis nodosa. Three patients had complete healing of the ulcers after about an average of 3 1/2 months of treatment with topical cyclosporine. Patient 4 had multiple ulcers over both his lower legs. Most of the ulcers in patient 4 healed after six months of treatment. One ulcer over his left foot only achieved 80% improvement after six months of therapy. None of the patients complained of any side effects. In all patients, pain was significantly reduced after two weeks of starting treatment. During treatment the blood investigations in all patients remained within normal limits and serum trough levels of cyclosporine were all within subtherapeutic range.

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Table I

Patient Sex/age	PG site	Duration of PG	Associated conditions	Previous treatment	Outcome
Pt 1 F/ 48yo (fig. 1)	Left lower leg	3 months	Rheumatoid arthritis	Prednisolone	Complete healing after 3 mths of therapy
Pt. 2 M/ 60yo (fig. 2)	Penile	1 1/2 years	None	Prednisolone Minocycline Intralesional triamcinolone	Complete healing after 4 mths after therapy
Pt.3 F/ 49yo (fig. 3)	Perineum	9 years	Behcets disease	Colchicine Sulphasalazine Dapsone Prednisolone	Complete healing after 3 mths of therapy
Pt. 4 M/ 50yo (fig. 4)	Lower legs	5 years	Cutaneous polyarteritis nodosa	Prednisolone Azathioprine Cyclophosphomide	Most ulcers healed after 6 mths of therapy. Only ulcer over left foot healed up to 80%

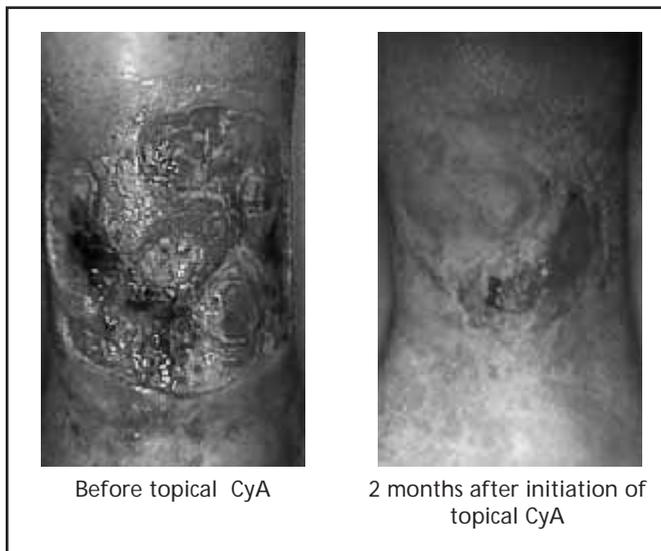


Fig. 1

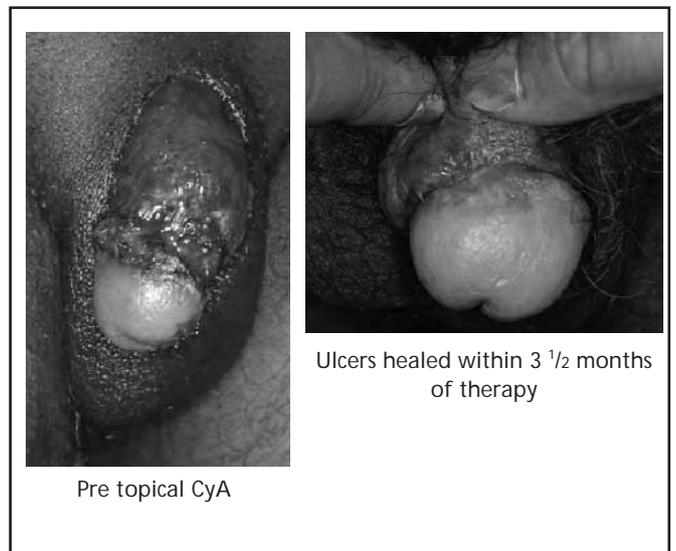


Fig. 2

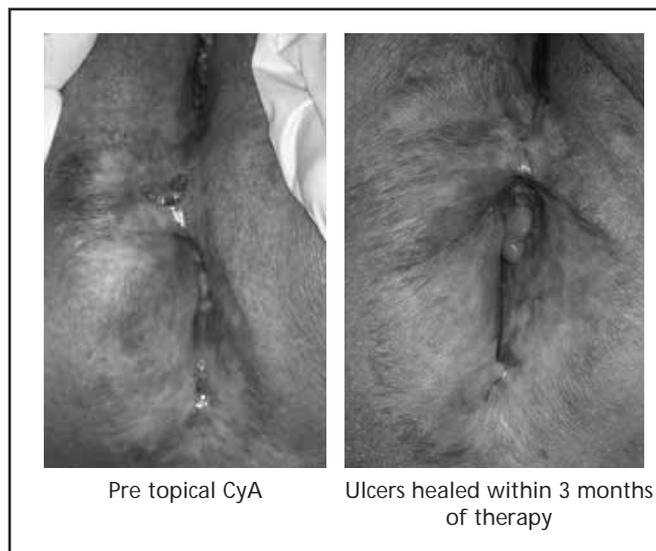


Fig. 3

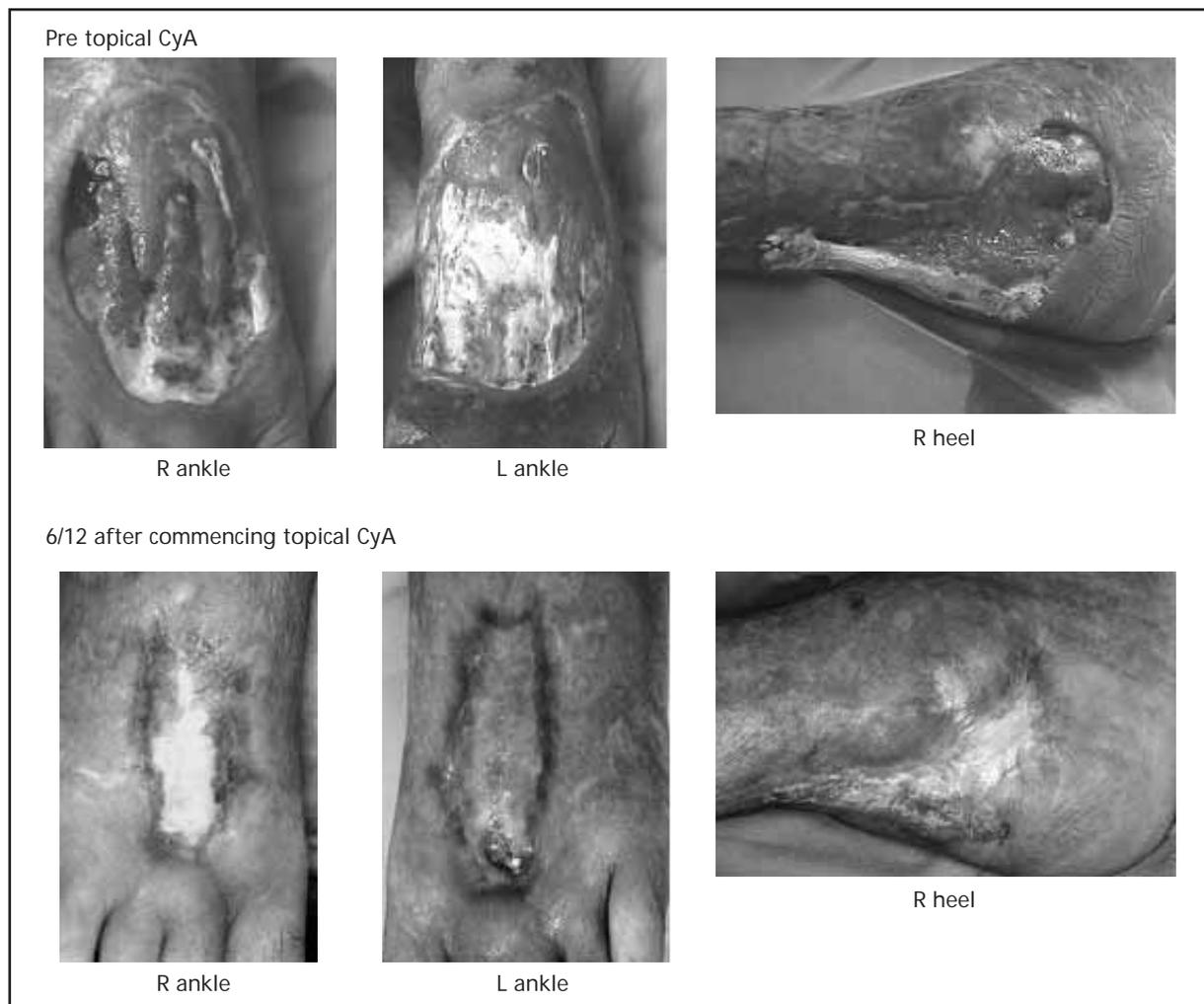


Fig. 4

**DISCUSSION**

Management of PG has always been a therapeutic challenge. Due to a lack of understanding of its origin and pathogenesis, various therapies have been used to treat PG. It is very important to have a logical approach to manage patients with pyoderma gangrenosum. Exclusion of other diagnoses such as bacterial pyoderma, deep fungal infection, mycobacterial infection, syphilitic gumma and factitial ulcer is mandatory. Management of underlying diseases, correction of anaemia, relief of pain, treating secondary infections and bed rest are also important<sup>3,4,5,6</sup>.

Conventional therapy for ulcerative PG is systemic immunosuppressant with local wound care. Systemic corticosteroid is the mainstay of therapy often requiring high dose of steroids and for a long duration of time<sup>3,4,5,6</sup>. This is associated with numerous complications and side-effects. Systemic cyclosporine has shown to be one of the most promising steroid sparing agents in the treatment of PG<sup>2,8,9</sup>. In 1985, Curley et al reported a patient with PG who responded well to cyclosporine<sup>2</sup>. Cyclosporine acts by selectively inhibiting the generation and proliferation of cytotoxic T lymphocytes while sparing T-suppressor cells. It

also inhibits the production and release of interleukin 2 and other lymphokines. However, systemic cyclosporine has multiple side-effects. The main life threatening side-effect is nephrotoxicity. Other serious side-effects include hypertension, hepatotoxicity and development of lymphomas<sup>2,8,9</sup>.

The use of a topical agent, reduces these systemic complication and is an attractive alternative in the management of PG. Topical tacrolimus (Protopic) is a more established form of topical therapy in PG as compared to topical cyclosporine<sup>12,13,14,15</sup>. In-vitro studies have shown that topical tacrolimus has a better skin absorption than topical cyclosporine as it has a lower molecular weight (882 kD for tacrolimus and 1202kD for cyclosporine) and is less lipophilic<sup>16</sup>. Topical cyclosporine has been used to treat for diseases that respond to systemic administration of the drug e.g atopic dermatitis and psoriasis but results have been disappointing<sup>17</sup>. These studies suggest that the ineffectiveness of topical cyclosporine may be attributed to its poor absorption capacity. However, topical cyclosporine has been shown to be beneficial as a therapy for oral lichen planus; the 'Swish and spit' technique<sup>11</sup>. To our knowledge, there has

only been one article in the English literature on the use of topical cyclosporine in PG. Mroweitz and Christophers in 1991 used intralesional cyclosporine on one patient with PG<sup>10</sup>. The major drawback of this technique was pain at the injection sites. In all four of our patients, instead of injecting cyclosporine, we applied it to the ulcer by using a piece of lint cloth. All the four patients with recalcitrant PG occurring at various sites (the lower legs, perineum and penile region) responded well with no side effects in particular pain was not documented with this technique. In fact, the pain that was normally associated with PG was significantly reduced immediately on initiation of the treatment. The exact mechanism of action of topical cyclosporine is unknown. In the absence of significant systemic absorption, the demonstrated effectiveness of topical cyclosporine in treating PG indicates that this compound may act by a local mechanism<sup>17</sup>. We postulate that topical cyclosporine acts by exerting a local immunomodulatory effect on these ulcers or by exhibiting its antibacterial properties.

No significant side effects was documented in all four patients. There was no substantive systemic absorption as observed by the serial serum cyclosporine levels measured in all of our patients. Therefore, we can avoid all the harmful effects and complications of systemic cyclosporine.

#### CONCLUSION

We have shown that topical cyclosporine is a novel and effective treatment for pyoderma gangrenosum. Topical cyclosporine is safe with no life threatening side effects. This approach allows reduction of severe adverse effects associated with systemic administration of cyclosporine including the complications of prolonged corticosteroid therapy. However, further controlled studies are necessary to establish and verify the efficacy and safety of topical cyclosporine in PG.

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