CASE REPORT

Topical timolol for the treatment of pyoderma gangrenosum

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SUMMARY

Treatment of pyoderma gangrenosum (PG) remains a challenge, and there are currently no specific or uniformly effective therapies. Although widespread or rapidly progressive disease often requires systemic treatment, localised and mild lesions may be effectively controlled with topical agents. The most frequently applied topical drugs are corticosteroids and calcineurin inhibitors. Recently, a patient with idiopathic PG of the lower limb was successfully treated with topical timolol and collagenase. Here, we report a case of a patient with collagenous colitis, ankylosing spondylitis and periumbilical PG. Persistent ulcerated skin lesions were successfully treated with topical timolol, although a flare of the underlying bowel disease temporarily interrupted the improvement. The case presented enhances the previously reported therapeutic potential of topical timolol in the treatment of PG. Control of chronic underlying disorders is critical to prevent rebound flares and maintain the benefit.

BACKGROUND

Treatment of pyoderma gangrenosum (PG) is challenging and, until now, no guidelines have been established. Although most therapies focus on reducing inflammation, an alternative approach emphasises antagonisation of keratinocyte β 2-adrenergic receptors (β 2-AR), in order to enhance keratinocyte migration and speed reepithelialisation.¹

CASE PRESENTATION

We present a 46-year-old woman with a history of collagenous colitis and ankylosing spondylitis with 6 years of evolution. Remission of articular and gastrointestinal diseases had been maintained, under treatment with budesonide, acemetacin, prednisolone and methotrexate.

For the past 3 years, the patient has been followed in the Dermatology Department for periumbilical PG, which had developed in a surgical site after cholecystectomy. Previous therapies included high-potency topical corticosteroids, topical calcineurin inhibitors and intralesional corticosteroid injections. Despite an initial response, progress had ceased and a localised and mild ulcerated lesion persisted in the past year (figure 1A).

TREATMENT

The patient started application of four drops of 0.5% timolol maleate ophthalmic solution on alternate days, and occlusion with alginate dressing after the solution had dried.

OUTCOME AND FOLLOW-UP

During the subsequent days, the wound rapidly improved such that, on treatment day 40, only millimetric erosions were observed (figure 1B). The patient maintained topical timolol application but, 23 days later, during a mild flare of gastrointestinal disease, an exacerbation of the skin lesions was noted, with development of small pustules that evolved to erosions (figure 1C). Timolol was maintained during the flare and gastrointestinal symptoms spontaneously improved. The patient received indication to continue the same treatment in PG lesions. At 125-day follow-up, periumbilical lesions demonstrated reepithelialisation (figure 1D). The patient reported that the wound had healed 1 month before, and she had discontinued timolol since then. No side effects were experienced during the treatment.

DISCUSSION

PG is an uncommon inflammatory skin disease with a chronic relapsing course, clinically characterised by painful, single or multiple ulcerated lesions, that often regresses with cribriform mutilating scars. Although pathophysiology is not completely understood, a genetic background and an altered immune and inflammatory response are certainly involved. PG is known to occur in association with several distinct diseases, mainly ulcerative colitis, Crohn's disease, seronegative arthritis, ankylosing spondylitis, rheumatoid arthritis, myeloproliferative disorders or monoclonal gammopathy.²

There are currently no specific or uniformly effective therapies for PG. Widespread or rapidly progressive disease usually requires systemic treatment, and the most frequently used drugs are oral corticosteroids and ciclosporin. Other oral and intravenous immunosuppressors, intravenous immunoglobulin and biological therapies have also been reported in the literature. Nevertheless, localised and mild PG may be effectively controlled using topical agents without incurring the side effects associated with systemic treatments. In most cases, the preference is for corticosteroids and calcineurin inhibitors.^{2 3}

Topical β 2-AR antagonists, such as timolol, have shown efficacy in ulcerated infantile haemangiomas, chronic venous leg ulcers and other recalcitrant wounds.⁴⁻⁷ Recently, a patient with idiopathic PG was successfully treated with timolol gel applied with collagenase ointment.¹ β -adrenergic receptors are present on cells in multiple organ systems, including the skin, particularly on

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Figure 1 Clinical feature of wound healing over time. (A) Day 0 of treatment. Persistent delayed healing. (B) Day 40 of treatment. Reepithelialisation of periumbilical wound. (C) Day 63 of treatment. Exacerbation with pustules and new erosions, during a flare of gastrointestinal disease. (D) Day 125 of follow-up. Sustained reepithelialisation of periumbilical lesions.

keratinocytes, fibroblasts and melanocytes. The mechanism of action of β_2 -AR antagonists appears to be related to enhancement of keratinocyte migration and promotion of wound healing.⁶ Neutrophils also express β_2 -AR, and reduction of neutrophil recruitment can represent another mechanism responsible for improvement of PG lesions.⁷

In our patient, despite an initial good response of ulcerated skin lesions with topical and intralesional corticosteroids and topical calcineurin inhibitors, the healing had ceased and no improvement had been observed in the past year. On the basis of the report of successful use of topical timolol for idiopathic PG of the lower limb, we discussed the possibility of using this off-label treatment with our patient and application was started on alternate days, for the convenience of the patient. Reepithelialisation was observed, confirming the promising results previously reported. A relatively long time for epithelialisation was needed (40 days), which could be a consequence of the application on alternate days instead of daily treatment and by potential absorption of the timolol solution into the alginate dressing, although the patient had been instructed to wait for the solution to dry, before to occlude with the dressing. A flare of bowel disorder inter-

rupted the benefit of timolol, but improvement was recovered after remission of gastrointestinal symptoms and with the maintenance of topical therapy.

In conclusion, in patients with PG and an underlying disorder, it is fundamental to control the associated condition, and in this scenery, skin disease often has a tendency to remit with the improvement of the underlying disorder. For those patients with persistent skin lesions, timolol may be a useful, inexpensive and non-invasive option. Nevertheless, controlled studies are needed to evaluate efficacy of topical timolol in PG, which is a limitation due to the low frequency of the disease.

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Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Treatment of pyoderma gangrenosum (PG) is challenging and, until now, no guidelines have been established.
- ▶ Although widespread or rapidly progressive disease usually requires systemic treatment, localised and mild lesions may be effectively controlled using topical agents without incurring the side effects associated with systemic therapies.
- ▶ Topical β_2 -AR antagonists enhance keratinocyte migration and speed reepithelialisation.
- ▶ Topical timolol may be a useful, inexpensive and non-invasive option for patients with PG.

REFERENCES

- 1 Liu DY, Fischer R, Fraga G, *et al.* Collagenase ointment and topical timolol gel for treating idiopathic pyoderma gangrenosum. *J Am Acad Dermatol* 2014;7:e225–6.
- 2 Gameiro A, Pereira N, Cardoso JC, *et al.* Pyoderma gangrenosum: challenges and solutions. *Clin Cosmet Investig Dermatol* 2015;8:285–93.
- 3 Thomas KS, Ormerod AD, Craig FE, *et al.* Clinical outcomes and response of patients applying topical therapy for pyoderma gangrenosum: a prospective cohort study. *J Am Acad Dermatol* 2016;75:940–9.
- 4 Weibel L, Barysch MJ, Scheer HS, *et al.* Topical timolol for infantile hemangiomas: evidence for efficacy and degree of systemic absorption. *Pediatr Dermatol* 2016;33:184–90.
- 5 Lev-Tov H, Dahle S, Moss J, *et al.* Successful treatment of a chronic venous leg ulcer using a topical beta-blocker. *J Am Acad Dermatol* 2013;69:204–5.
- 6 Braun LR, Lamel SA, Richmond NA, *et al.* Topical timolol for recalcitrant wounds. *JAMA Dermatol* 2013;149:1400–2.
- 7 Tang JC, Dosaj J, Kirsner RS. Topical timolol for a refractory wound. *Dermatol Surg* 2012;38:135–8.

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