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CASE REPORT

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Whether to maintain or strengthen the treatment for pyoderma gangrenosum ulcerative type may depend on the response after two to four-week treatment intervention: The outcome of three cases with details clinical course

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Abstract

Determining whether the treatment intensity needs to be increased or can be maintained at a constant level may be suggested after 2–4 weeks of treatment. The use of TNF-α inhibitor, removal of necrotic tissue, and skin grafting may promote epithelialization.

KEYWORDS

adalimumab, adverse effect, corticosteroid, pyoderma gangrenosum, treatment strategy

1 | INTRODUCTION

Pyoderma gangrenosum is relatively rare inflammatory skin disease causing progressive necrotic ulceration. TNF-α inhibitor would be efficient, and response of the ulcer after 2–4 weeks of treatment should play a role in determining whether the treatment intensity needs to be increased or can be maintained at a constant level

Pyoderma gangrenosum (PG) is a rare inflammatory skin disease that causes progressive necrotic ulceration, mainly on the lower extremities and trunk.[1] The ulcerative (classic) PG is the most common type and is treated by the administration of a systemic corticosteroid, prednisolone 0.4–0.5 mg/kg/day, as the first-line therapy.[1,2] Systemic corticosteroids play a significant role in facilitating wound healing in PG; however, many cases are unresponsive, and long-term use of corticosteroids likely causes adverse effects.[1,3] Large ulcers generally take a long time to heal. Hence, surgical treatment may be considered once the ulcer activity has become clinically quiescent, although surgery may worsen PG.[1] Tumor necrosis factor (TNF)-α inhibitors have been suggested to be effective for PG,[4,5] and adalimumab has recently been approved in Japan for the treatment of PG.[5] Studies have shown that refractory ulcers treated with adalimumab responded within two weeks, and epithelialization was achieved in 54% of patients within 26 weeks.[5] However, it is not clear which stages of PG can be treated by TNF-α inhibitors. It is also not clear whether treatment intensity should be maintained at a current level or strengthened over time.

In the current study, we present three cases of PG with large ulcers and report detailed clinical progress and outcomes. We focused on a single ulcerated lesion for each PG patient and compared rates of healing between treatment

with prednisolone and that with a combination of prednisolone and adalimumab together with debridement and skin grafting.

2 | CASE REPORT

2.1 | Case 1

A 62-year-old woman was referred to our department with a complaint of an ulcer on the left lower extremity that had persisted for one year after a minor injury. She had a history of rheumatoid arthritis for 30 years and was taking 3.75 mg of prednisolone daily and 3 mg of methotrexate weekly. She had never smoked before. A bacterial culture ruled out any skin infections. C-reactive protein (CRP) levels were mildly elevated (0.42 mg/dl). After confirming a diagnosis of PG by skin biopsy, we started treatment with 20 mg (0.5 mg/kg) of prednisolone daily, starting on week 4 after referral to our department. From week 8, the amount of prednisolone was decreased gradually, and methotrexate was started, gradually increasing from 8 mg weekly. CRP levels decreased to normal range by week 12 (baseline: 0.42 mg/dl; week 12: 0.10 mg/dl). A reduction in the ulcer area was not observed until week 20 (at this time, she was receiving 7 mg of prednisolone daily and 10 mg of methotrexate weekly). At week 24, the ulcer size was further decreased. By the end of week 36, 50% of the ulcer remained (at this time, she was receiving 5 mg of prednisolone daily and 12 mg of methotrexate weekly; Figure 1).

2.2 | Case 2

A 79-year-old woman was referred to our department with a complaint of an ulcer on the left lower leg. The ulcer had appeared 6 month previously without any triggers. She had a history of rheumatoid arthritis for 40 years and was taking 4 mg of methotrexate weekly. She had never smoked before. On physical examination, an ulcer on the left lower extremity was confirmed. Her CRP levels were mildly elevated (0.55 mg/dl). Although chemical debridement for the thick necrotic tissue was performed (week 4), the ulcer size remained unchanged by week 12. Treatment with prednisolone (20 mg daily; 0.5 mg/kg) was started in week 16, but no reduction in the size of the ulcer was observed two weeks later. Surgical debridement therapy and skin grafting were therefore performed in week 20 (at this time, CRP levels were 0.04 mg/dl). The ulcer relapsed two months after the operation (week 28). Treatment with adalimumab (40 mg weekly) was started in week 32. Her CRP levels decreased to normal range immediately after starting adalimumab (week 28: 0.23 mg/dl; week 32: 0.04 mg/dl; Figure 2).

2.3 | Case 3

An 81-year-old woman was diagnosed with PG 2 years ago. She had a history of rheumatoid arthritis for 10 years and was taking 5 mg (0.1 mg/kg) of prednisolone daily, 6 mg of methotrexate weekly, and 25 mg of etanercept weekly. She had never smoked before. On physical examination, a large ulcer was observed on the left lower extremity. A bacterial culture excluded any skin infections. We switched the TNF-α inhibitor from etanercept to adalimumab. CRP levels decreased after starting adalimumab (baseline: 4.54 mg/dl; week 12: 0.28 mg/dl; Figure 3). The ulcer size remained unchanged until week 12; however, after the removal of necrotic tissue in week 20, the ulcer improved significantly through weeks 24 to 76. At week 76, the patient was receiving 40 mg of adalimumab weekly, and no relapse has been observed.

3 | DISCUSSION

An intermediate dose of systemic corticosteroids has long been used for the treatment of PG; however, due to their serious adverse effects,[13] the treatment has shifted to the use of the safer and more effective adalimumab.

During the phase 3 trial of adalimumab, 22 PG patients received concomitant use of corticosteroids at

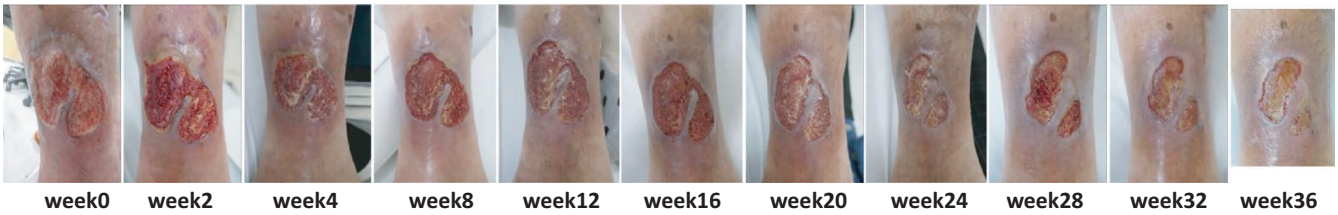

FIGURE 1 A 62-year-old woman presented an ulcer on the left lower extremity. We started treatment with 20 mg (0.5 mg/kg) of prednisolone daily, starting on week 4. From week 8, the amount of prednisolone was decreased gradually, and methotrexate was started, gradually increasing from 8 mg weekly. A reduction in the ulcer area was not observed until week 20. At week 24, the ulcer size was further decreased. By the end of week 36, 50% of the ulcer remained

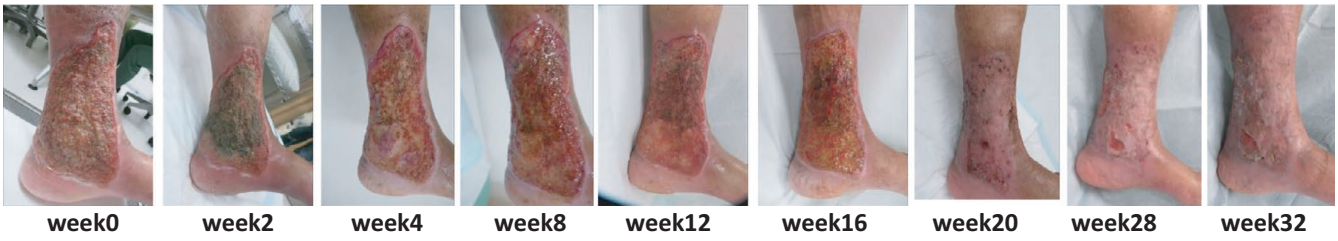

FIGURE 2 A 79-year-old woman was referred to our department with an ulcer on the left lower leg. Treatment with prednisolone (20 mg daily) was started in week 16, but no reduction in the size of the ulcer was observed two weeks later. Surgical debridement and skin grafting were performed in week 20. The ulcer relapsed two months after the operation (week 28). Treatment with adalimumab (40 mg weekly) was started in week 32

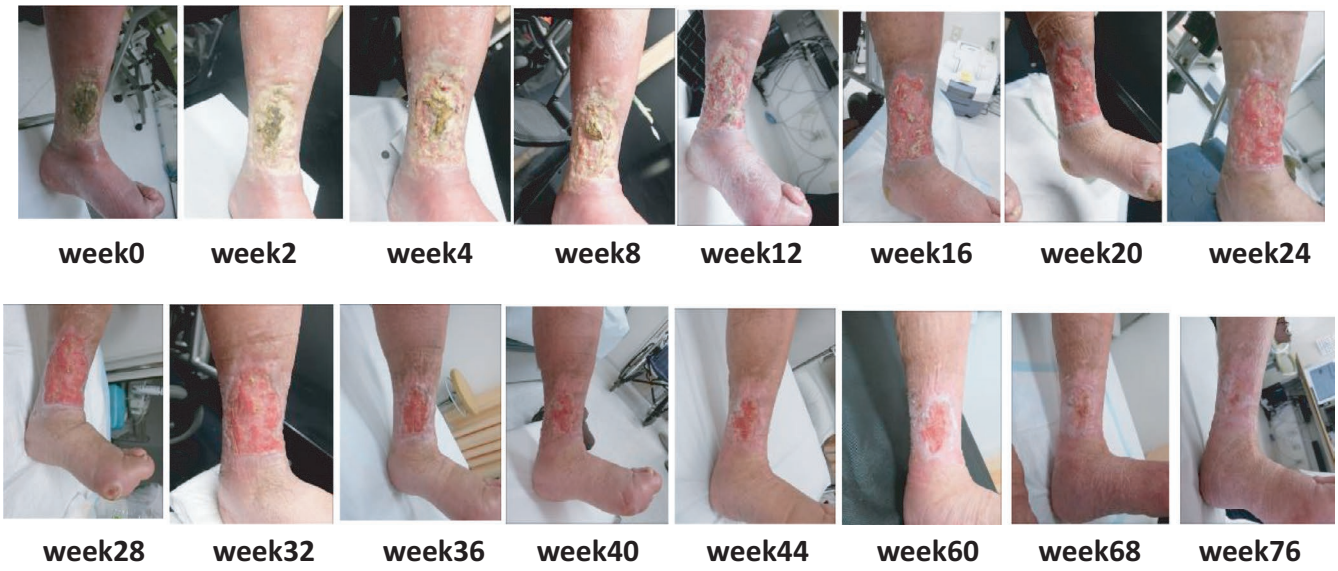

FIGURE 3 An 81-year-old woman with a large ulcer on the left lower extremity. She was taking 5 mg of prednisolone daily, 6 mg of methotrexate weekly, and 25 mg of etanercept weekly for rheumatoid arthritis. We switched the TNF-α inhibitor to adalimumab. The ulcer size remained unchanged until week 12. However, after the removal of necrotic tissue in week 20, the ulcer improved significantly through weeks 24–76. At week 76, the patient was receiving 40 mg of adalimumab weekly, no recurrence has been detected

prednisolone-equivalent doses of 10 mg/day or less. This trial was conducted to evaluate the efficacy and safety of adalimumab for active ulcers. Ulcers were shown to reduce in size in the 2 weeks after the administration of adalimumab. A reduction rate of −22.3% at week 2, −31.8% at week 6, and −63.8% at week 26 was observed. The mean rate of healing was −0.21 cm^2/day for the first 6 weeks.[5] A separate study reported the mean rate of healing using prednisolone (0.75 mg/kg/day) as −0.14 cm^2/day for the first 6 weeks.[6] Although these were not direct comparative study between TNF-α inhibitors and prednisolone, the data suggest that adalimumab shows superior efficacy compared to the usual prednisolone treatment in terms of the healing speed of ulcers.

In case 1, we started treatment with prednisolone; however, no reduction in the ulcer area was seen in the initial 20 weeks, although CRP levels decreased to normal range. At week 24, the ulcer size had decreased; however, 9 month after starting oral prednisolone, 50% of the ulcer remained. Although this patient chose not to receive treatment with TNF-α inhibitors, the poor response to normal prednisolone treatment was evident within the initial 2–4 weeks of treatment. In such cases, changing the treatment strategy might be considered after 2–4 weeks.

In case 2, thick necrotic tissue was observed with the absence of any local infection. Chemical debridement of the necrotic tissue did not reduce the size of the ulcer. Two weeks after starting 20 mg of prednisolone daily, the ulcer remained unchanged, although CRP levels became normal. Surgical debridement therapy and skin grafting were then performed; however, two months after the operation, the ulcer relapsed and CRP levels increased. Treatment with 40 mg of adalimumab weekly was started 4 weeks later, and her CRP levels decreased to the normal range.

In case 3, the CRP levels decreased after starting adalimumab. However, the ulcer only started to improve significantly 4 weeks after the removal of necrotic tissue. In

this case, the ulcer was particularly large and took 2 years to heal. With long-lasting ulcers, such as this, a skin graft should be considered once the ulcer activity has decreased in order to quicken healing.

The use of TNF-α inhibitors entail risks such as infections, transaminitis, demyelinating disease, lupus-like syndrome, and malignancy. However, these risks are relatively low compared to those associated with the use of a systemic corticosteroid.[1] The risks of long-term use of a systemic corticosteroid include osteopenia, weight gain, glaucoma, cataracts, hyperglycemia and diabetes, Cushing's syndrome, immunosuppression, adrenal insufficiency, and corticosteroid psychosis.[1] Furthermore, chronic systemic corticosteroid use is known to impair wound healing in the perioperative period.[3] The strength of the treatment option needs to be reconsidered if the ulcer activity continues for longer than 4 weeks or if the ulcer size remains unchanged. Debridement of necrotic tissue might also be considered to promote epithelialization. TNF-α inhibitors may be particularly useful for intractable PG with large ulcers, and it may sometimes be beneficial to combine TNF-α inhibitors with a skin graft.

4 | CONCLUSION

It is expected that a TNF-α inhibitor, such as adalimumab, would be more efficient in treating PG than a systemic corticosteroid. We suggest that the response of the ulcer after 2–4 weeks of treatment should play a role in determining whether the treatment intensity needs to be increased or can be maintained at a constant level. We further suggest that in cases of large PG ulcers, the removal of necrotic tissue may promote epithelialization. Finally, large ulcers could also be treated with a TNF-α inhibitor, such as adalimumab, along with a skin graft to promote quicker healing.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

YN, conceptualization, project administration, writing - original draft; TA, writing - original draft; SI, supervision; KH, supervision; NY, supervision; YM, supervision; YN, supervision; MK, supervision; KY, conceptualization, project administration, writing - review & editing.

ETHICAL STATEMENT

The research was conducted in accordance with the Declaration of Helsinki. The patients have given their written informed consent to publish their case including publication of images. The need for approval of this study protocol was waived by Mie University Hospital Internal Review Board.

DATA AVAILABILITY STATEMENT

The patients data is not publicly available on legal or ethical grounds.

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