Resolution of therapy-resistant pyoderma gangrenosum with upadacitinib

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INTRODUCTION

Janus kinase (JAK) inhibitors, orally or topically administered, are a relatively new therapeutic option for several immune-driven dermatologic diseases (including atopic dermatitis, psoriasis, alopecia areata, and vitiligo). In the future, we may be able to expand its indications with therapy-resistant pyoderma gangrenosum (PG). Because PG is often challenging to treat because of therapy resistance, frequent relapses, and varying results of the sparse (and mostly off-label) treatment options, there is a clear need for additional therapeutic options.

Abbreviations used:

COP: cryptogenic organizing pneumonia
JAK: janus kinase
PG: pyoderma gangrenosum
SpA: spondyloarthritis

CASE REPORT

In 2017, a 65-year-old woman with HLA-B27−negative spondylarthritis (SpA) (under treatment with methotrexate [15 mg/wk] and infliximab [5 mg/kg/8 wk]) presented with a painful, non-healing wound around an abdominal surgery scar diagnosed as PG. Insufficient improvement with topical steroids and tacrolimus combined with systemic minocycline (200 mg/d) led to administration of systemic corticosteroids (methylprednisolone up to 32 mg/d). Infliximab was stopped later that year because of cryptogenic organizing pneumonia (COP), potentially tumor necrosis factor-α inhibitor induced. After discontinuation of infliximab and slow tapering of methylprednisolone, complete healing of PG was achieved. Because of relapse of SpA activity, etanercept (50 mg/wk) was started. During that time, recurrence of PG manifested as extremely painful purpuric papulopustules on medial sides of the lower portion of both legs with frequent sanguinopurulent drainage. Histologic examination was compatible with PG. Treatment with doxycycline (200 mg/d), colchicine (2 mg/d), and azithromycin (3 × 500 mg/wk) yielded an insufficient response. Only prednisone at ≥ 10 mg/d provided some relief. Because of the recurrence of COP and further deterioration of PG, etanercept was discontinued. Anti-TNF therapy was then considered as a possible trigger and/or sustaining factor for the development of COP and PG. However, deterioration of her PG continued over the years. Cyclosporine was then started, with some improvement, but had to be quickly discontinued because of renal function deterioration and hypertension. Subsequently, even more painful purpuric and tense papulonodules developed on the lower portion of her legs (Fig 1, *A*). During this period, secukinumab (150 mg/4 wk) and apremilast (2 × 30 mg/d) were consecutively given for her SpA but were discontinued because of insufficient disease control and side effects. A skin biopsy was repeated to exclude

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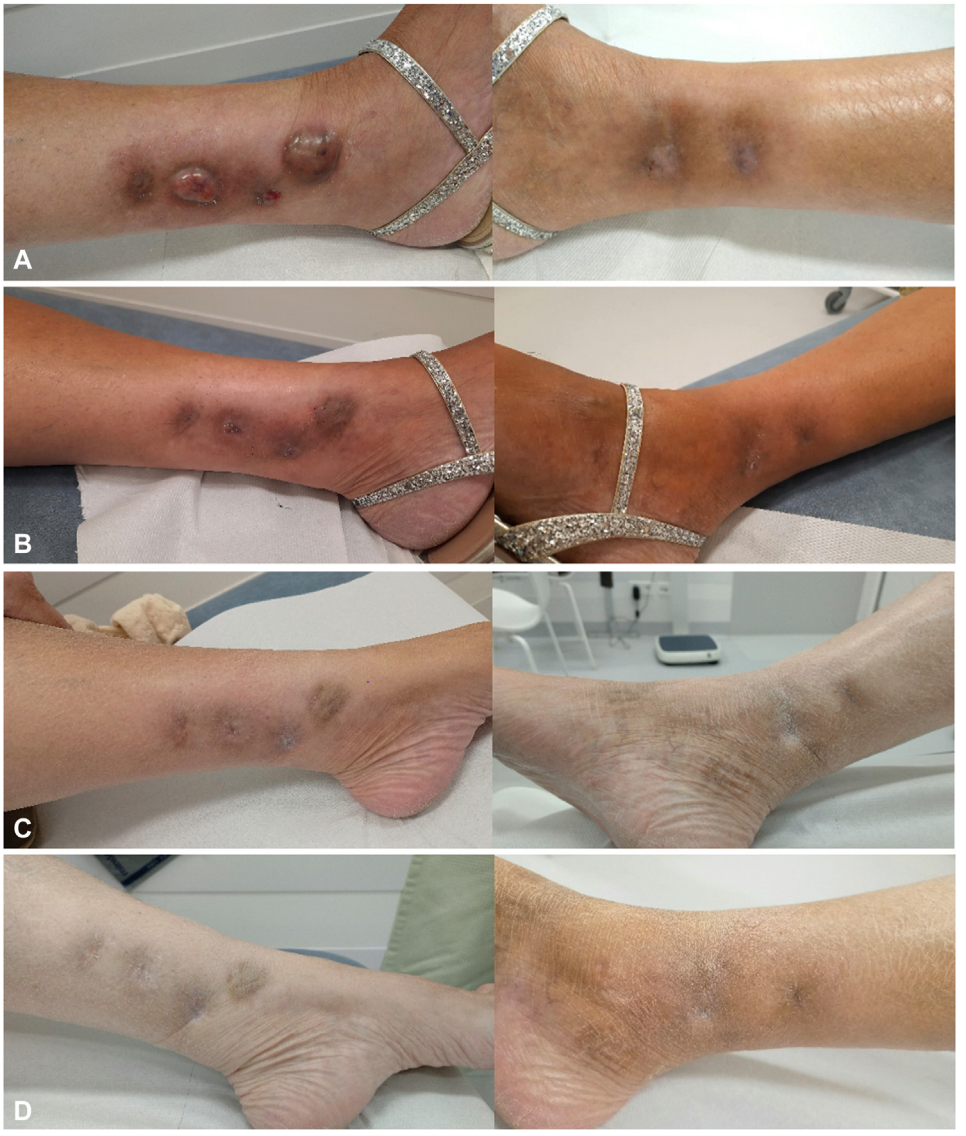

Fig 1. A, Pyoderma gangrenosum lesions before start upadacitinib. **B,** Pyoderma lesions 6 weeks after start upadacitinib. **C,** Pyoderma lesions 12 weeks after start upadacitinib. **D,** Pyoderma lesions 24 weeks after start upadacitinib.

a chronic infectious process or malignancy. Histologic examination found necrotic debris in the dermis with surrounding inflammatory infiltrate containing inflammatory cells, including neutrophilic granulocytes. Cultures and polymerase chain reaction for deep mycosis and mycobacterial infections proved negative. Shortly after this skin biopsy, upadacitinib (Rinvoq; AbbVie; 15 mg/d) was started because of persistent inadequate control of SpA. This resulted in spectacular improvement of PG and SpA activity at follow-up after 6 weeks (Fig 1, *B*). Complete remission was seen at follow-up after 12 weeks and persisted after 24 weeks, with only residual pigmentation (Fig 1, *C* and *D*). Upadacitinib was well tolerated, and prednisone intake could be reduced to 3 mg/d.

DISCUSSION

PG is a neutrophilic dermatosis with an incompletely understood pathogenesis. It involves dysregulation of both innate and adaptive immunity, leading to a neutrophil-rich autoinflammatory process with the elevation of multiple cytokines. Some of these cytokines act through the JAK/STAT pathway.[1] The importance of the JAK/STAT pathway in PG has also been demonstrated through immunohistochemistry in skin biopsy specimens.[2,3]

JAK inhibitors are administered orally, which make them easy to use. They seem to have an acceptable safety profile[4]; nevertheless, the European Medicines Agency recently recommended limited use in high-risk populations because of an increased risk of serious cardiovascular problems, venous thromboembolism, cancer, serious infections, and mortality.[5] These observations, however, are based on data with tofacitinib in a high-risk population and may not apply to all JAK inhibitors. Further research and pharmacovigilance are needed to determine the long-term side effects and necessary monitoring/follow-up. Presumably, JAK-1 selectivity provides a better safety profile than less selective JAK inhibitors.[6]

Upadacitinib is JAK-1 selective[6] and is already in use for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, and colitis ulcerosa. By presenting this case of recalcitrant PG spectacularly improving after treatment with upadacitinib, we may expand its (off-label) indications. Other JAK inhibitors, including tofacitinib, ruxolitinib, and baricitinib, have also shown promising results in previously published cases.[1,2,7] However, given the preferred safety profile of JAK-1 inhibition, upadacitinib may be preferred. Recently, another case with upadacitinib was published.[8] It involved a 50-year-old woman with rheumatoid arthritis–associated PG, situated on the lower portion of both legs. After 2 weeks of treatment, there was a marked improvement in skin lesions. After 14 weeks, PG was no longer active.

Case reports with emerging therapies are important for rare, difficult-to-treat conditions, such as PG, because management guidelines are based on scarce evidence available (primarily deriving from case reports and case series). With this case report, we hope to broaden the therapeutic options for PG and stimulate further research to determine the place of JAK inhibitors in PG treatment.

Conflicts of interest

None disclosed.

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