Anakinra for recalcitrant pyoderma gangrenosum: a case series

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Abstract

Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis characterized by rapidly enlarging, painful ulcers. Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that blocks the activity of IL-1α and IL-1β by competitively inhibiting IL-1 binding to the IL-1 type I receptor. We present a series of two patients with recalcitrant PG, who had limited therapeutic options due to multiple previous treatment failures and multiple co-morbidities, who obtained 100% healing with anakinra. Compared to conventional first-line therapies for PG, the safety profile of anakinra may be preferable for patients with multiple co-morbidities. Further research is needed to assess the safety and efficacy of anakinra for PG.

Six learning points

- Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis characterized by rapidly enlarging, painful ulcers.
- Half of patients with PG have an underlying inflammatory disease – approximately 30% have inflammatory bowel disease, 10% have inflammatory arthritis, 5% have haematological malignancy, and 5% have solid organ malignancy.
• Patients with PG in the United Kingdom have been shown to have a three-fold increased risk of premature death.
• Several monogenic autoinflammatory diseases associated with PG are caused by mutations which upregulate the activity of Interleukin-1 (IL-1), such as PSTPIP1, causing PAPA syndrome and PASH syndrome.
• Anakinra is a recombinant IL-1 receptor antagonist that blocks the activity IL-1α and IL-1β by competitively inhibiting IL-1 binding to the IL-1 type I receptor, which is expressed in a wide variety of tissues and organs.
• The safety profile of anakinra may be preferable to conventional treatments, such as corticosteroids or ciclosporin, for patients with multiple co-morbidities, but further research is needed to assess the safety and efficacy of anakinra for PG.

Introduction
Pyoderma gangrenosum (PG) is an autoinflammatory neutrophilic dermatosis characterized by rapidly enlarging, painful ulcers. ¹ Half of patients with PG have an underlying inflammatory disease. ² Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that blocks the activity of IL-1α and IL-1β. ³ We present a series of two patients treated with anakinra for recalcitrant PG.

Report
Patient one, a 51-year-old woman with a history of obesity, was referred with painful inframammary and inguinal ulceration (Figure 1). Skin biopsy showed neutrophilic infiltration of the epidermis, consistent with PG. Haematological workup detected positive lupus anticoagulant, β2-glycoprotein and anti-cardiolipin antibodies, consistent with antiphospholipid syndrome, in the context of three previous miscarriages. There was no family history of neutrophilic dermatoses.
Therapy with prednisolone 80mg produced rapid clinical improvement. However, relapse occurred with minimal reduction in dosage. Ciclosporin provided modest effect and was withdrawn after one month due to nephrotoxicity. Infliximab was stopped following secondary failure. Complications related to these therapies had included recurrent herpes zoster, multidrug-resistant urinary tract infections, and steroid-induced diabetes mellitus. Inpatient hospital admission was required for intravenous methylprednisolone, followed by intravenous immunoglobulin (IVIG) and rituximab infusions, which delivered significant benefit for almost one year. At that time, her disease relapsed severely, and rituximab and IVIG were stopped.

Mycophenolate mofetil and doxycycline were trialled with minimal effect. The patient’s quality of life had deteriorated substantially and she required assisted accommodation due to immobility. Due to progressive disease, with an associated renal injury requiring dialysis, further inpatient admission was required for intravenous methylprednisolone. Efficacy was achieved with oral cyclophosphamide but this was stopped after nine months due to nausea and concerns about long term safety.

Given her treatment-resistant disease, therapy with anakinra was initiated, with four weeks of loading at 2mg/kg daily, followed by 100mg once daily. This agent had a rapid and profound effect on symptoms, with 100% healing after four months of treatment. Clinical improvement facilitated a slow withdrawal of prednisolone after four years of continuous oral steroid therapy. Iatrogenic diabetes requiring insulin has reversed and the patient is now off all diabetic medication. She intentionally lost 22kg in the first four months of treatment. Her PG remains in remission, 24 months following initiation of interleukin-1 blockade.

Patient two, a 67-year-old woman, was referred with severe painful lower limb ulceration (Figure 2). She was on adalimumab and methotrexate for rheumatoid arthritis (RA). She also had a history of chronic kidney disease, hypertension, peripheral vascular disease, and dyslipidaemia. Oral prednisolone was started at 45mg daily with good initial effect. However, she was admitted to the hospital with an upper gastrointestinal bleed the following month. Upper GI endoscopy showed gastric and duodenal ulceration. Second line therapeutic strategies were limited by multiple co-morbidities. There was concern about prescribing ciclosporin given her pre-existing renal disease. The patient declined
infliximab infusions because she was unable to access regular transport to hospital. Due to her severe disease, her multiple co-morbidities, and the fact that anakinra is licensed for RA, anakinra was introduced and adalimumab and methotrexate were stopped. Her PG slowly stabilized, with 50% reduction in ulcer size after six months, and 100% healing after 12 months. Repeat upper GI endoscopy showed healing of her peptic ulcers following two months of proton pump inhibition. Oral prednisolone was tapered to stop over eight months. Both her PG and RA remain quiescent 24 months following initiation of interleukin-1 blockade.

Discussion
Pyoderma gangrenosum is a rare disease with an incompletely understood aetiology. A 2018 Delphi exercise has provided updated diagnostic criteria for PG. Misdiagnosis is frequent and associated conditions often go undetected. Treatment of PG remains largely anecdotal, with only two published randomised controlled trials. With no national or international guidelines, management is challenging. Treatment choice is based on the severity and extent of PG, and patient co-morbidities. Up to 30% of patients with PG have underlying inflammatory bowel disease (IBD), although Langan et al detected a rate of 20% in the UK population. Pustular and peristomal variants are more commonly seen with IBD. Inflammatory arthritis is present in approximately 10%. Solid organ malignancy is seen in 5%. Haematological malignancy is present in under 5% of patients, and is more frequently associated with the bullous variant. PG can be seen in up to 15% of patients with antiphospholipid syndrome, with localized thrombosis thought to precipitate the secondary inflammatory reaction. Other conditions such as cryoglobulinaemia are only rarely associated. A three-fold increased risk of premature death has been identified in patients with PG in the UK. Currently, PG is considered a neutrophil-mediated autoinflammatory disease, involving aberrant activation of the inflammasome. This is supported by recent studies which provide novel insight to innate immune system mutations and upregulation of the Janus kinase signalling pathway in lesional skin. Other factors include involvement of the adaptive immune system, external triggers such as pathergy, and genetic predisposition. It is poorly understood how these factors interact to influence the disease.
Several monogenic autoinflammatory diseases associated with PG are caused by mutations which upregulate activity of Interleukin-1, such as PSTPIP1, causing PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne); and PASH syndrome (pyoderma gangrenosum, acne, and hidradenitis suppurativa). The PSTPIP1 mutant inhibits the anti-inflammatory effect of pyrin, leading to release of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα, further amplifying the inflammatory response. These conditions respond favourably to IL-1 blockade, providing a theoretical basis for the use of anakinra in non-syndromic PG. Other case series have highlighted the role of IL-1 driven inflammation in autoimmune disease–associated PG.

Our case series shows that excellent response to anakinra can be seen despite multiple previous drug failures. Conventional first-line therapies for PG such as high-dose corticosteroids, ciclosporin, and TNFα inhibition may be problematic due to adverse events in the context of other inflammatory conditions or co-morbidities. However, anakinra is associated with low rates of serious adverse events. Further research is needed to assess the safety and efficacy of anakinra for non-syndromic PG.

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**Figure Legends**

**Figure 1A**
Multiple ulcerations with violaceous undermined edges on the breast and inframammary area.

**Figure 1B**
Extensive ulceration in the inguinal folds with slough.

**Figure 2**
Deep ulceration on the pretibial area with an undermined violaceous edge and granulation tissue.
