

REVIEW

Pyoderma gangrenosum: a review of the clinical, mechanistic and therapeutic landscape

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Abstract

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that is uncommon and can sometimes be associated with systemic diseases. The pathophysiology underlying this condition is poorly understood, although recent advances suggest that local cutaneous abnormalities and functionally abnormal neutrophils may trigger ongoing innate and adaptive immune system activity. PG remains a difficult condition to diagnose, mainly because it was previously seen as a diagnosis of exclusion, although newer diagnostic criteria have been proposed in order to overcome this. Furthermore, many patients do not respond to conventional therapy for PG once diagnosed, and experience persistence or worsening of their condition over time. The advent of immune targeted therapies, however, may represent a new treatment option for these patients. This review focuses on the clinical features and diagnosis of PG, as well as providing an update in our understanding of the pathophysiology and treatment options available for this debilitating condition.

Keywords pyoderma gangrenosum, inflammation, Th17, neutrophils

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Introduction

Pyoderma gangrenosum (PG) is a painful and ulcerative condition that is classified as a neutrophilic dermatosis. It is an uncommon disease, with a worldwide incidence of approximately 3–10 cases per million population per year¹. Although it may occur at any age, it is mostly seen in those between 20–50 years of age, with females being affected slightly more than males.

The condition was first described in 1908 by Louis Brocq, and named as pyoderma gangrenosum in 1930 by Brunsting et al.². The term ‘pyoderma’ refers to a purulent infection of the skin, whilst ‘gangrenosum’ refers to the extensive necrosis seen in these ulcers. It was later found, however, that these ulcers are primarily aseptic in nature, and hence the condition being referred to as ‘pyoderma’ is a misnomer.

The pathophysiology underlying PG is yet to be known, although it may occur secondary to other inflammatory diseases. PG was previously thought to arise from a functional disorder of neutrophils, although recent advances

suggest there is also adaptive and innate immune system dysregulation, as well as local cutaneous abnormalities.

Due to the lack of understanding behind how PG develops, there is yet to be a highly effective treatment which targets biological pathways. Current management involves optimal wound care and topical or systemic steroids or steroid sparing agents. Certain biological agents, including IL-23 and IL-17 antagonists, as well as JAK-STAT inhibitors, however, may hold promise in the rapid treatment of this condition.

Clinical features

PG most commonly occurs on the lower extremities, although other areas, including the trunk, abdomen, scalp and face, may be affected. It may also affect extra-cutaneous locations, including the lungs, eyes and mouth (termed pyostomatitis vegetans)³.

Up to 25% of patients affected with PG will experience ‘pathergy’ or the Koebner phenomenon⁴. This occurs when localised trauma causes worsening of existing PG or the formation of new PG lesions. The mechanism underlying

pathergy remains poorly understood, although a similar process has also been described in Behcet's disease⁵.

Subtypes

Ulcerative PG (classic form)

This type of PG initially starts as either a deep and tender nodule or a superficial pustule which undergoes necrosis and ulceration, usually over the course of a few days⁶. Following this, the ulcer may follow one of two clinical courses. It may either rapidly expand to involve previously unaffected surrounding tissue, along with severe pain and systemic symptoms⁶. Alternatively, it may gradually spread over the course of months, with some areas undergoing spontaneous resolution, and other areas undergoing further growth⁶.

During ulcer expansion, the border is often elevated with an undermined edge, and has a dull red or violaceous appearance (Figure 1A). An erythematous 'halo' may be seen surrounding this border, signalling active inflammation in adjacent areas of skin. The base of the ulcer is usually necrotic and has purulent exudate or small abscesses⁶.

Pustular PG

Pustular PG is characterised by crops of painful pustules which, unlike ulcerative PG, do not undergo ulcer formation⁷. The pustules are usually accompanied with fevers, arthralgias and joint effusions⁷. This form of PG also appears to be

associated with ulcerative colitis (UC)⁷. Pustular PG severity does not appear to be related to UC severity however, and treatment of the UC does not necessarily improve the PG⁸.

Bullous PG

Also known as atypical PG, this form is characterised by rapid superficial skin necrosis with overlying blister formation⁹. A grey hue is often noted in surrounding tissue, and the lesions are painful; rupture or removal of the bulla may reveal a superficial ulcer (Figure 1B). The bullae are typically located on the arms and face, as opposed to the lower extremities⁹. It has been reported in patients with haematological disorders⁹.

Sweet's syndrome (acute febrile neutrophilic dermatosis) is believed to be on the same spectrum as bullous PG as it too can present with superficial erosions⁹. However, Sweet's syndrome lesions present as plaques or nodules and, unlike PG, lack a violaceous undermined border¹⁰.

Vegetative PG

Vegetative PG is characterised by a verrucous appearance, with shallow ulcers that lack an undermining border and which usually have no purulent exudate within the base (Figure 1C). They are usually located on the head and neck region and are usually indolent in nature⁹. There is, however, a rare and more aggressive form of vegetative PG known as malignant PG. Whilst these ulcers are also located on



Figure 1. Types of PG

A=ulcerative (classic) PG on the lower leg

B=bullous PG on the dorsal hand, rapidly progressing to an undermined violaceous-bordered painful ulcer

C=painful PG lesions on the buttock of an individual with hidradenitis suppurativa and IBD, and a verrucous plaque of vegetative PG on the lateral ankle

D=peristomal PG in the setting of Crohn's disease

the head and neck, they rapidly expand and may erode underlying structures including the parotid gland¹¹.

Peristomal PG

This type of PG occurs in patients who have an ileostomy or colostomy for underlying inflammatory bowel disease (IBD). It is localised to surrounding areas of the stoma (Figure 1D) and is believed to occur due to ongoing irritation from faecal material passing through the stoma, or from adhesives that are used to attach the stoma bag to the stoma itself.

Systemic associations

Approximately 25–50% of patients with PG will have an underlying inflammatory systemic disease. The systemic disease may be subclinical, and may occur before or after the onset of PG. It is therefore important to appropriately investigate and monitor patients with PG for these conditions.

IBD is the most commonly associated disease, with one study finding it present in 41% of PG patients¹². Although the exact reason behind this association remains unknown, common gene mutations in PG and IBD have been identified with respect to antigen presentation and cytokine signalling, including *TIMP3* and *IL8RA*¹³. Furthermore, alterations in the Wnt signalling pathway, which is known to occur within the intestinal tract of IBD patients¹⁴, may also be occurring within PG ulcers. The Wnt pathway is crucial in maintaining epidermal stem cells for reepithelisation during tissue damage¹⁴. Wnt signalling has been found to be suppressed in the wounds of diabetic patients^{15,16}, and a similar process may be occurring in PG, although further studies are required. Interestingly, PG activity does not necessarily correlate with the activity of underlying IBD, and suppression of IBD will not necessarily lead to a reduction in PG activity or ulceration.

Rheumatoid arthritis also affects approximately 8.5% of patients with PG¹². Other inflammatory arthritis that has been associated with PG include psoriatic arthritis, ankylosing spondylitis and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome, albeit at a much lower rate.

A vast range of haematological malignancies have also been associated with PG, including monoclonal gammopathy, myeloma, leukaemia, lymphoma and myelodysplasia¹². PG as a paraneoplastic phenomenon has also been described in the literature, including in cancer and neuroendocrine tumours^{17,18}.

Associated syndromes

Certain autoinflammatory syndromes are characterised by the presence of PG. The mechanism underlying these syndromes appears to be mediated by the over-expression of IL-1B¹⁹. IL-1B causes the release of inflammatory cytokines including TNF- α , IFN- γ , IL-8 and Regulated on Activation, Normal T-Cell Expressed and Secreted (RANTES)²⁰. IL-1B also prevents apoptosis of neutrophils, enabling for ongoing tissue destruction²¹.

Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) syndrome is associated with mutations in the *PSTPIP1* gene²² which enables overactivation of the inflammasome and subsequent cleavage of pro IL-1B into IL-1B²³. The syndrome is characterised by a recurring, sterile, monoarticular arthritis along with severe nodulocystic acne and PG²³.

Pyoderma gangrenosum, Acne and Suppurative Hidradenitis (PASH) syndrome may be associated with CCTG motif repeats near the *PSTPIP1* promoter region¹⁹, again enabling for overactivation of the inflammasome. However, there is new evidence to suggest that the cause is polygenic²⁴.

Pyogenic Arthritis, Acne, Pyoderma gangrenosum and Suppurative Hidradenitis (PAPASH) is another rare syndrome that lacks genetic studies, although a p.E227D missense mutation within exon 10 and 11 of the *PSTPIP1* gene has been identified within one patient¹⁹. The significance of this mutation is unknown, and further studies in patients are required.

Diagnosis and investigations

The diagnosis of PG can often be challenging, with many cases being initially misdiagnosed²⁵. This is because PG shares some overlapping features with other diseases, and there are no diagnostic histological or laboratory investigations. PG has traditionally been a diagnosis of exclusion although, recently, there have been two proposed criteria for PG diagnosis known as the Delphi consensus and the PARACELSUS score.

The Delphi consensus (Table 1) has a sensitivity of 86% and specificity of 90%²⁶. It requires identification of neutrophilic infiltrate within biopsy of the ulcer edge as its sole major criteria²⁶. At least four of the eight minor criteria must also be satisfied, including pathergy, exclusion of infection, a history of IBD or inflammatory arthritis, ulceration of a papule/pustule/vesicle within 4 days of appearance, undermining border/peripheral erythema/ulcer tenderness, presence of multiple ulcers with at least one being on the anterior lower leg, cribriform scarring, or a reduction in ulcer size 1 month after commencing immunosuppressants²⁶.

The histological requirement of a neutrophilic infiltrate for PG in the DELPHI criteria has been subject to criticism, as these findings are usually present in the acute phase of PG²⁷. A retrospective study identified only 7% of PG patients had this characteristic finding²⁸. Furthermore, with respect to cribriform scarring being part of the DELPHI minor criteria, one recent study analysing 62 PG scars identified no evidence of any cribriform type scarring, suggesting that it may not actually be associated with PG²⁹.

The PARACELSUS scoring system (Table 2) requires at least 10 points for the diagnosis of PG³⁰. There are three major criteria each assigned three points, and include disease progression, exclusion of differential diagnosis and a reddish violaceous wound border³⁰. The minor criteria assigned two points include responsiveness to immunosuppression,

irregular ulcer shape, pain greater than 4 on visual analogue scale, or localisation of PG at sites of trauma³⁰. Additional criteria are worth one point and include undermined wound border, systemic disease involvement and presence of suppurative inflammation³⁰. Overall sensitivity and specificity data for this scoring system has not been stated.

Regardless of the criteria used, a biopsy is highly recommended in order to help exclude other conditions with a similar clinical appearance²⁵. Whilst a biopsy does risk pathology if the lesion is truly PG, it is generally outweighed by the need to reach an accurate diagnosis and commence appropriate treatment²⁵.

Other relevant investigations

Patients with PG may have leucocytosis and elevated inflammatory markers including C-reactive protein and

Table 1. The Delphi consensus for the diagnosis of ulcerative PG²⁶

Criteria type and feature
Major criteria (required)
Neutrophilic infiltrate present on biopsy of ulcer edge
Minor criteria (four of eight required)
Exclusion of infection on histology
Pathergy
Presence or history of IBD
Presence or history of inflammatory arthritis
Papule/pustule/vesicle that ulcerates within 4 days of appearance
Peripheral erythema, undermining border and tenderness at ulcer site
Multiple ulcers, with at least one on anterior lower leg
Reduction in ulcer size within 1 month of immunosuppressive therapy

Table 2. The PARACELsus score for the diagnosis of PG³⁰: a score of 10 or above indicates that PG is highly likely

Criteria type, points assigned per feature and feature
Major criteria – 3 points
Rapidly progressive course
Reddish-violaceous border
Exclusion of differential diagnosis
Minor criteria – 2 points
Responsive to immunosuppressive therapy
Irregular ulcer shape
Pain score >4/10 on visual analogue scale
Presence of ulcer at size of trauma (i.e. pathergy)
Additional criteria – 1 point
Undermined wound border
Suppurative inflammation on histology
Presence of systemic disease

erythrocyte sedimentation rate⁶. Swabs for culture should also be taken from PG ulcers, although growth may be indicative of a secondary wound colonisation rather than infection.

Further investigations may also be necessary if an underlying systemic disease is suspected⁶. Patients who have features suggestive of IBD should be promptly referred to a gastroenterologist for consideration of a colonoscopy and further management. Those with features of inflammatory arthropathy should be referred to a rheumatologist, along with testing for rheumatoid factor and anti-cyclic citrullinated peptide antibodies. If a haematological malignancy is considered, serum protein electrophoresis and serum and urine immunoelectrophoresis may also assist in the diagnosis.

Although less common, systemic lupus erythematosus³¹ and vasculitis³² may also cause PG, in which case anti-nuclear antibodies and anti-neutrophilic cytoplasmic antibodies should be performed.

Differential diagnosis

The differential diagnosis is broad, and includes conditions that may present with ulceration. These include vascular occlusion and venous ulcers, malignancies (including primary cutaneous lymphomas), systemic vasculitis (including granulomatosis with polyangiitis), cutaneous infections, external trauma, drug reactions and other neutrophilic dermatoses.

Pathophysiology

The exact mechanism through which PG arises remains poorly understood³³. The rapidly progressive and ulcerative nature of this disease from seemingly ‘normal’ skin makes it difficult to identify early initiating events that may lead to downstream inflammatory cascades³³. Histologically, neutrophils are known to predominate within established PG, but it is unknown whether their presence is due to primary neutrophilic abnormalities or is secondary to an already established complex immunological dysfunction³⁴.

Neutrophil activity in PG

During infections, neutrophils normally function to produce extracellular traps, a meshwork consisting of chromatin fibres and degradative enzymes which trap and destroy microbes. Neutrophil extracellular traps (NETs) have been found to be elevated, particularly within the serum of patients with syndromic forms of PG^{35,36}. The neutrophils are functionally abnormal in that there is an enhanced propensity for spontaneous NET formation and reduced ability to degrade NETs³⁵. The ongoing presence of NETs within tissue may prime B cells to produce autoantibodies against certain NET components as seen within other conditions such as hidradenitis suppurativa, and thus cause antibody mediated inflammation³⁷.

A variety of cytokines related to neutrophil activity have also been identified in PG tissue. Dermal fibroblasts, endothelial

cells and other local immune cells may be releasing IL-8 which serves as a chemoattractant for circulating neutrophils^{20,38}. The increased expression of chemokine (C-X-C motif) ligand (CXCL) 1/2/3, CXCL16 and RANTES allows for circulating neutrophils to migrate through the vascular endothelium into PG tissue^{20,39,40}, whilst TNF- α ³⁹ and C5a⁴¹ enables sustenance and amplification of neutrophilic activity. Once neutrophils enter the tissue, destruction and ulceration is likely facilitated through the over expression of metalloproteinases including MMP-2 and MMP-8 which disrupts the extracellular matrix^{20,39,42} and leads to necrosis.

Adaptive immune system activity

The Th17 pathway has been strongly associated with PG activity. This has been identified through the overexpression of IL-17 and its receptor within PG tissue from multiple translational studies^{35,38,39}, as well as through the rapid and sustained clinical improvement seen with IL-23 and IL-17 antagonists within PG case reports^{43–45}. It is possible that Th17 may also be activated through the release of IL-9 from local Th9 cells (as seen with other inflammatory dermatoses)⁴⁶, in addition to IL-23 pathways.

IL-12 has also been identified to be expressed in PG tissue, likely leading to the stimulation of the Th1 response and subsequent release of IFN- γ and CXCR3, enabling for leucocyte recruitment and differentiation^{38,47}. Similarly, elevated IL-4 levels within tissue may be driving Th2 differentiation, causing IL-5, IL-13 and CCR3 release⁴⁷. These cytokines are known to stimulate B cells to produce antibodies, including IgA and IgE, which may contribute to further tissue destruction.

Regulatory T-cell (Treg) activity may also be reduced within PG lesions, with a reduction in the FOXP3/ROR γ t ratio, TGF- β /CD4+ ratio and IL-10/CD4+ ratio being identified within one translational study⁴⁸. The increased Th1, Th2 and Th17 response coupled with reduced Treg activity indicates that T-cell-mediated inflammation plays a substantial role in PG pathogenesis.

Follicular adnexal structures in PG

PG ulcers generally do not affect areas of the body lacking follicular adnexal structures, including the palms and soles³³. Areas of skin that have previously been affected by PG and have undergone fibrosis (along with an absence of follicular adnexal structures), also appear to be resistant to PG re-ulceration³³. It is possible that the development of auto-antigens to components of the follicular adnexa may be a key initiating event for the development of PG³³. The lack of CD34+ (fibroblast) cells identified in PG scar biopsies³³ when compared to active PG ulcers may indicate that fibroblasts play an inflammatory role in active PG ulceration.

Gene expression studies

The recent use of RNA sequencing has enabled for an analysis of gene expression studies in patients with PG when compared to healthy controls. One recent study of eight PG

patients with perilesional biopsies identified 5,762 genes that were differentially expressed to a significant extent when compared to healthy control biopsies⁴⁹. Furthermore, within perilesional PG tissue of these patients, there was a large upregulation of inflammatory cytokine related genes in the dermis and a downregulation of these genes in the epidermis⁴⁹. Several inflammatory and trafficking pathways have been identified within this study which may play a role in PG pathogenesis, although further studies are required to more comprehensively characterise this⁴⁹.

Treatment

There is yet to be a universal, standardised treatment approach for PG. Whilst a range of topical and systemic therapeutic options are available, they have all demonstrated variable success across patients.

Stratification of PG into mild, moderate and severe forms may assist in treatment choice. The number and location of PG ulcers, ulcer size, rate of ulcer expansion, as well as extracutaneous PG involvement, should all be considered when determining disease severity. If PG has occurred secondary to a systemic disease, then it is imperative that the systemic disease is adequately treated, as this too may lead to ulcer improvement. A combination of local and systemic treatments, along with regular wound care, has been found to confer the highest likelihood of adequate ulcer healing⁵⁰.

Topical therapies

Topical treatments include tacrolimus ointment 0.1% or super potent topical steroids, including clobetasol propionate^{51,52}. Tacrolimus is a calcineurin inhibitor and functions by inhibiting the expression or transcription of genes encoding IL-2, IL-3, IL-4, IL-8, TNF- α and granulocyte-macrophage colony stimulating factor (GM-CSF)⁵³. These cytokines are predominant in T-cell activation and cytotoxicity⁵⁴, hence their inhibition enables for a dampening of the inflammatory response seen within PG ulcers. A study comparing these two treatments for peristomal PG found that topical tacrolimus was associated with a higher rate of PG healing⁵⁵. Intralesional steroid injections with triamcinolone acetonide 6–40mg/L into the active borders of the PG ulcer may also halt ulcer expansion and promote healing⁵⁶.

Systemic therapies

With regards to systemic therapies, oral prednisolone and cyclosporine are the most commonly used first line treatments. Oral prednisolone is typically commenced at 0.5–1mg/kg whilst cyclosporine is dosed at 3–5mg/kg, with both being found to have approximately the same rate of ulcer healing 6 weeks post-initiation⁵⁷. Where prednisolone is being used as a first line agent, the dosage may be weaned once appropriate control of PG has been achieved, with consideration of transitioning to a steroid sparing agent including cyclosporine, azathioprine, mycophenolate mofetil or methotrexate. Other anti-inflammatory adjunctive agents, including colchicine, dapsone and tetracyclines,

have been used as part of combination systemic therapy for moderate to severe PG. In cases of rapidly progressive PG, the use of intravenous corticosteroids, including pulsed methylprednisolone or intravenous immunoglobulin (IVIG), may be considered⁵⁸.

Biological therapies

Biological therapies are a suitable option for PG refractory to systemic and topical therapies. Due to the rarity of PG, the use of biological agents has been mostly limited to small observational studies or case reports. Hence, further studies are required to further evaluate their efficacy in treating this condition.

TNF-α antagonists have been the most widely studied agent for PG as they are also commonly used to treat coexisting IBD. Infliximab, adalimumab and etanercept have all demonstrated efficacy through a reduction in ulcer size and improvement in related symptoms⁵⁹⁻⁶¹.

IL-23 inhibitors, including ustekinumab (IL-12/IL23p40) and guselkumab, as well as IL-17 inhibitors, including brodalumab, have also demonstrated effectiveness in PG ulcer healing⁴³⁻⁴⁵. This is likely due to inhibition of the Th17 axis which has been implicated as a major contributor to PG pathogenesis.

JAK-STAT inhibitors, including tofacitinib, may represent a new and effective treatment option for PG as they are able to downregulate the production of multiple associated cytokines including IL-23R, IL-12R, and IL-10R. One study of three patients with PG associated with Crohn’s disease and inflammatory arthritis found marked ulcer healing and symptoms improvement within 12 weeks of treatment with tofacitinib⁶².

Table 3. Treatment options available for different types of PG

Wound care	Local treatments	Systemic (non-biological) treatments	Biological agents
Exudative PG⁶⁴			
Alginates / foam	Tacrolimus ointment 0.1% ⁵²	Oral prednisolone	TNF-α antagonists (e.g. infliximab) ⁵⁹
Granulating or epithelialising PG⁶⁴			
Collagen-based dressings	Topical corticosteroids ⁵¹ <ul style="list-style-type: none"> • Clobetasol propionate • Betamethasone dipropionate in an optimised vehicle 	Steroid sparing agents ⁶⁶ <ul style="list-style-type: none"> • Cyclosporine • Prednisone • Azathioprine • Mycophenolate mofetil • Methotrexate 	IL-23 antagonists (limited evidence to date) ^{43,44}
PG ulcers with secondary colonisation⁶⁴			
Silver sulfadiazine	Intralesional steroid injections at active ulcer edge ⁶⁶	Colchicine ⁶⁶ Tetracyclines ⁶⁶ Dapsone ⁶⁶	JAK/STAT inhibitors ⁶²
PG ulcers with surrounding swelling⁶⁴			
Compression bandages	–	Intravenous immunoglobulin (IVIG) ⁶⁶	–

Wound care

Whilst there are no specific guidelines for optimal wound care in PG, the main goals are to protect the ulcers from experiencing further physical trauma and fostering a microenvironment that enables wound healing. The type of dressings used may be guided by the tissue, infection, moisture balance and edge advancement (TIME) approach for chronic wounds⁶³ (Table 3).

Active ulcers will usually produce large amounts of exudate due to high neutrophil activity, which leaves the surrounding normal skin at risk of maceration and infection. Alginate dressings enable for high amounts of fluid absorption whilst still providing adequate moisture to the wound⁶⁴. Foam dressings are useful for affected areas of skin that may be subject to physical trauma, although their absorptive ability is lower than alginates⁶⁴. PG wounds that are epithelising or granulating will benefit from collagen-based dressings as they lower protease activity⁶⁴, absorb exudate and promote collagen deposition, whilst still maintaining a moist environment. Hydrocolloid-based dressings are useful for healing PG ulcers that have overlying eschar formation as they stimulate enzymatic degradation of the eschar and this enables for effective re-epithelisation within the wound bed⁶⁴.

PG wounds are also often susceptible to secondary colonisation and infection, mainly from bacteria, including *Staphylococcus aureus*, coagulase negative staphylococci and *Peptostreptococcus* species⁶⁵. If this occurs, antimicrobial dressings including those containing silver, will reduce the bacterial load due to its ability to damage the bacterial cell wall and membrane⁶⁴. Topical antibiotics should generally be avoided to prevent the development of resistance.

PG ulcers on the lower legs may lead to the development of oedema secondary to ongoing inflammation. In such cases, gentle compression stockings or wraps, along with leg elevation, may reduce the oedema⁶⁴.

Conclusion

To date, PG remains a difficult condition to diagnose and treat. The development of diagnostic criteria, including Delphi and PARACELSUS, may assist clinicians in more effectively identifying this condition. Whilst significant advances have been made in the pathophysiology underlying PG, there is a need to further characterise molecular events that occur prior and during the early development of lesions. With regards to treatment, biological therapies trialled in a minority of PG patients, such as IL-23 and IL-17 antagonists, have shown promise and may be useful in patients who are not responding to conventional therapy. Clinical translational trials are needed in the future in order to determine whether suppression of the Th17 axis will lead to a downregulation of genes associated with inflammatory pathways, ideally by comparing pre- and post-treatment perilesional samples in PG patients.

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Conflict of interest

JWF has conducted advisory work for Janssen, Boehringer-Ingelheim, Pfizer, Kyowa Kirin, LEO Pharms, Regeneron and UCB, participated in trials for UCB, Pfizer and Eli Lilly, and received research support from Ortho Dermatologics.

Ethics statement

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