THERAPY IN PRACTICE

Pyoderma Gangrenosum: Treatment Options

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Abstract

Pyoderma gangrenosum is a rare neutrophilic dermatosis that leads to exceedingly painful ulcerations of the skin. Although the exact pathogenesis is not yet fully understood, various auto-inflammatory phenomena with increased neutrophil granulocyte activity have been demonstrated. Despite the limited understanding of the pathogenesis, it is no longer a diagnosis of exclusion, as it can now be made on the basis of validated scoring systems. However, therapy remains a major multidisciplinary challenge. Various immunosuppressive and immunomodulatory therapies are available for the treatment of affected patients. In addition, concomitant topical pharmacologic therapy, wound management and pain control should always be addressed. Corticosteroids and/or cyclosporine remain the systemic therapeutics of choice for most patients. However, in recent years, there has been an increasing number of studies on the positive effects of biologic therapies such as inhibitors of tumour necrosis factor-α; interleukin-1, interleukin-17, interleukin-23 or complement factor C5a. Biologics have now become the drug of choice in certain scenarios, particularly in patients with underlying inflammatory comorbidities, and are increasingly used at an early stage in the disease rather than in therapy refractory patients.

1 Introduction

Pyoderma gangrenosum (PG) is an ulcerative inflammatory skin disease classified within the neutrophilic dermatoses group. It is a rare disease with a prevalence of 5.8 cases per 100,000 adults [1, 2]. PG negatively impacts quality of life and carries a three times higher mortality risk than that of the general population [3]. The classic clinical presentation are very painful skin ulcers with a predilection for the lower extremities in approximately 80% of cases [2, 4, 5] (Fig. 1). When the lower extremities are involved, it is particularly important to fully evaluate for other causes of skin ulceration. For example, venous and arterial status must be assessed, and frequent evaluation for infection is necessary. In addition, skin biopsy can rule out many other differential diagnoses. However, any hair-bearing skin on the body has the potential to develop PG. Less common presentations including bullous, verrucous and pustular variants have been described [6]. Other ulcerative variants include peristomal PG. In the initially acute inflammatory stage of classic PG, patients often have an erythematous papule or pustule that rapidly develops into a painful skin ulceration or multiple ulcerations with gunmetal grey borders and violaceous erythema. Once the acute inflammation has subsided,

large wounds may also present without classic or distinctive features, making the diagnosis even more challenging [6]. The pathergy phenomenon has been reported in up to 30% of patients with PG and describes the formation of new ulcers after minor trauma (e.g. needle injury). Sometimes this is a clinical clue for the diagnosis of PG; however, it is not specific to PG and has also been described in other patients with auto-inflammatory or neutrophilic conditions [7].

PG still represents a diagnostic challenge, as it is a rare disease with several clinical mimickers. With a misdiagnosis rate of up to 39%, it is considered the prototype of misdiagnosis among other skin ulcerations where the initial diagnosis was PG [8]. The most common clinical mimickers are venous leg ulcers, vasculitis, vasculopathies and factitial ulcers (Table 1). Recent efforts from clinical researchers, including experts worldwide, have supported the implementation of diagnostic frameworks to improve this critical issue in clinical practice. Three diagnostic criteria have been proposed: the Su and Delphi consensus, and the PARACELSUS score. All these diagnostic criteria seem to be useful in clinical practice, but the PARACELSUS score has shown the highest sensitivity among comparative studies [9, 10]. However, the specificity of all of them remains relatively low. The classic histological findings in PG have been well described. In early pustules or ulcerations, diffuse neutrophilic infiltrates are found around hair follicles [11]. However, this inflammatory infiltrate evolves into a non-specific inflammatory infiltrate (e.g. lymphohistiocytic

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Key Points

Systemic therapy with corticosteroids and/or cyclosporine remains the treatment of choice for most patients with pyoderma gangrenosum.

Based on new data, systemic therapies with biologics are gaining importance as alternative or first-line therapy in patients with inflammatory comorbidities.

Concomitant topical therapy can be given with classic immunosuppressants, e.g. corticosteroids or calcineurin inhibitors.

There should always be a special focus on pain management.

Figure 1 Very painful pyoderma gangrenosum on the extensor side of the lower leg.

infiltrate) once the ulceration becomes chronic. In two retrospective chart reviews of patients with PG, characteristic biopsy findings of PG were reported in only 7% (8 of 103) and 11% (5 of 47), respectively [4, 9]. PG is often associated with other inflammatory disorders such as inflammatory bowel disease (IBD 13.0–22.7%) and rheumatoid arthritis (RA 9.2–16.9%) [12–14]. It is also important to note that PG does not reflect the clinical course of the underlying disease, and it is not uncommon for patients with PG to have well-controlled IBD or vice versa [14]. Some patients also have underlying haematologic disorders (monoclonal gammopathy of unknown significance) or malignancies (leukaemias or other neoplasia) [15, 16]. Despite these comorbidities being clinical clues in the diagnosis and workup for PG, they seem to have a more preponderant role in the prognosis and/or selection an appropriate therapeutic approach [17] (Fig. 2). Besides medical management to control the associated comorbidity and the inflammation inherent to PG with either local pharmacologic therapy and/or systemic therapy, wound care management and pain control also needs to be addressed throughout the treatment course.

2 Drug-Induced Pyoderma Gangrenosum

The occurrence of PG after taking drugs has been repeatedly reported in the literature (Table 2). Although the underlying pathomechanisms are not clearly known, it must be assumed that a dysregulated inflammatory reaction with disturbed migration and activation of neutrophil granulocytes also occurs as a result of the drugs in genetically predisposed individuals. Keratinocyte apoptosis and alteration of epigenetic mechanisms might play a role as well [18]. A direct assessment of the causal relationship of the intake of a drug and the induction of a PG is not always easy and reports

with drug rechallenge are rare. Mostly, these are descriptions of single patients. Many of those patients had an underlying disease such as (haematologic) neoplasia or a chronic inflammatory disease [19]. Thus, it cannot always be said with certainty whether the drug was the trigger for the PG or whether the disease would have occurred even without the drug. Another important aspect is the temporal relationship between the start of drug therapy and the occurrence of PG. Very different time periods have been described [20, 21]. For example, if a large proportion of the world's population received appropriate vaccinations during the Covid-19 pandemic, the temporal context would include patients with PG [22]. It is then only possible to determine whether clustering has occurred by analysing large patient collectives. In the context of rarely occurring PG, however, these are exclusively individual case descriptions, which in principle, could also be random. However, other immune-mediated clinical diseases were also found significantly more frequently in association with the Covid-19 vaccinations, so a connection could certainly exist here [23].

In the first study summarising drug-induced PG, colony-stimulating factors (CSFs) and tyrosine kinase inhibitors (TKIs) were the most common culprits [18]. CSFs are haematopoietic growth factors used for chemotherapy-induced bone marrow suppression and have been reported as possible culprits since the 1990s [24, 25]. TKIs are small molecules used as targeted therapy in several cancers; the most

Table 1 Selection of clinical mimickers of pyoderma gangrenosum.

Most common

Venous leg ulcer

Vasculopathies: livedoid vasculopathy, calciphylaxis, Martorell hypertensive ulcer

Vasculitis: granulomatosis with polyangiitis, cutaneous leucocytoclastic vasculitis

Factitial ulcers (dermatitis artefacta)

Less common

Other neutrophilic diseases: Behcet's disease, neutrophilic dermatosis of the dorsal hands (NDDH), erosive pustular dermatoses

Non-melanoma skin cancer: basal cell cancer, squamous cell cancer, cutaneous lymphomas (particularly primary cutaneous anaplastic large cell lymphoma), cutaneous leukaemias, cutaneous metastasis

Rare

Inflammatory dermatoses: ulcerative necrobiosis lipoidica, ulcerative panniculitides

Infectious diseases: leishmaniasis, atypical mycobacterium (e.g. buruli ulcer), deep fungal infection (e.g. blastomycosis), herpes panniculitis

common culprit in drug-induced PG within this group has been sunitinib [26]. Subsequently, in an analysis of 44 publications with 52 cases of drug-induced PG based on the Naranjo criteria [19], the most common probable culprits were cocaine and levamisole. The anthelmintic agent levamisole is often added to cocaine because it is an inexpensive additive that prolongs the effects of cocaine. Levamisole is known to alter the chemotaxis response of neutrophils. In addition, levamisole and cocaine can increase inflammation and autoimmunity [27]. Reviewing the list of drugs that have been implicated in causing PG, it is striking that these are often medicaments that have otherwise been successfully used for PG therapy. These paradoxical reactions have already been described for various other autoimmunological disease patterns, such as psoriasis, hidradenitis suppurativa or inflammatory bowel diseases [28, 29]. They begin a few weeks to months after the start of biologic therapy and resolve after discontinuation of the drugs without specific therapy [30]. In an analysis of all case reports in which PG was thought to have been triggered by the administration
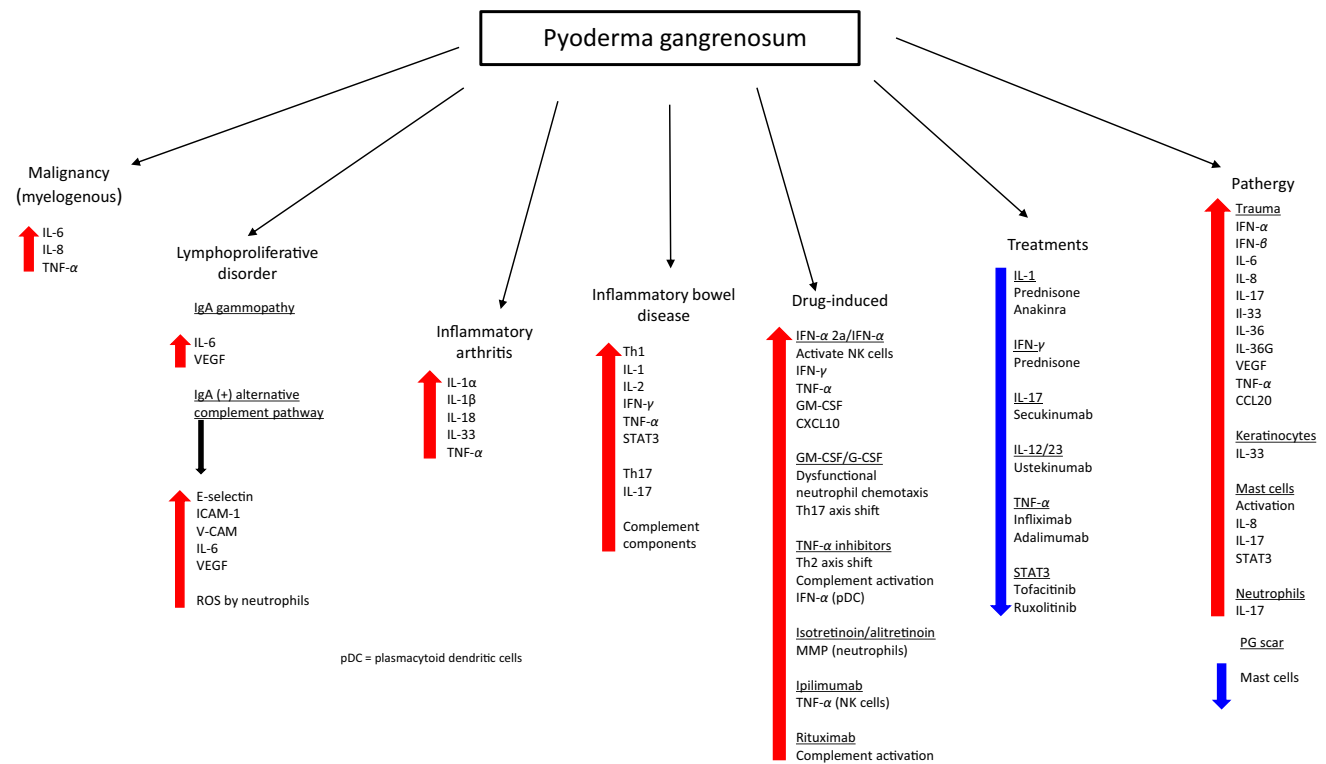

Figure 2 Pathophysiological aspects in pyoderma gangrenosum.

Table 2 Drugs that can induce pyoderma gangrenosum.

Antibodies

Interleukin inhibitors

Brodalumab

Dupilumab

Secukinumab

Tocilizumab

TNF-α inhibitors

Adalimumab

Certolizumab

Etanercept

Infliximab

Anti-CD-20 antibodies

Ocrelizumab

Rituximab

Integrin antagonist

Vedolizumab

VEGF-inhibitor

Bevacizumab

Immune checkpoint inhibitors

Abatacept

Ipilimumab

Pembrolizumab

Targeted therapies

Tyrosine kinase inhibitors

Cabozantinib

Gefitinib

Ibrutinib

Imatinib

Pazopanib

Sunitinib

BRAF/MEK inhibitor

Dabrafenib and Trametinib

Diabetes therapeutics

Dulaglutide

Insulin

Retinoids

Alitretinoin

Isotretinoin

Other

Azacitidine

Cocaine/levamisole

COVID-19 vaccine

Granulocyte colony-stimulating factor (G-CSF)

Hydralazine

Interferon-alpha2b

Lenalidomide

Propylthiouracil

Sulpiride

Injection site only

Enoxaparin

Erythropoietin

of biological therapy, 57 patients were identified. Here, 41 cases involved rituximab, 12 cases involved TNF-α inhibitors, 3 cases involved interleukin 17A and one case involved cytotoxic T-lymphocyte-associated protein 4 antibodies [31]. It is hypothesised that in these paradoxical reactions, there is a shift of the cytokine balance towards a molecular pattern typical of the respective induced disease. Looking more closely at the case reports, almost all published patients had systemic inflammatory diseases. Therefore, it is important to consider that the PG was possibly not induced by the biologic therapy but rather the biologic did not sufficiently suppress the induction of PG. After discontinuation of the drugs, other immunosuppressive or immunomodulatory therapies were almost always used, so the improvement of the PG could also be attributed to the newly initiated therapies.

Interestingly, some of the drugs are administered by injection. Here, it must be clarified whether the drug or a pathergy phenomenon related to the physical stimulus was causally responsible. If, for example, PG occurs at the injection site of enoxaparin [32] or erythropoietin [33], it must be assumed that the pathergy phenomenon was more likely the contributing factor. Interestingly, for azacitidine, the occurrence of a PG has been described both at the injection site [34] and independently [35]. Drug-induced PG is diagnostically challenging and often seen in the presence of other predisposing causes (e.g. underlying inflammatory conditions). Meaningful testing or other direct detection methods have not yet been developed. It is therefore very important to recognise the potential association and avoid the triggering drugs if possible.

3 Topical and Locally Administered Therapies

Once the diagnosis of PG has been established, the objective clinical features of severity for PG such as ulcer size, depth, number and location can guide the next steps. Patients with PG often present to clinicians at a late stage with ulceration, and the focus is placed on systemic therapies to gain rapid control of the inflammation. However, a subset of patients might present with early and small ulcerations, e.g. patients who are having a recurrence, and be in a position to start local treatment early in the course of the disease. Based on our experience, small PG ulcers (4 cm^2 or less) without compromise of the deep structures (e.g. muscle/tendon) might be ideal for trying local or intra-lesional immunosuppressants. Since local therapy can help limit the dose and duration of systemic therapeutics, they can be useful throughout the entire treatment period.

3.1 Standard Local Therapy

The two most commonly used local therapies are super potent corticosteroids and calcineurin antagonists [36]. Corticosteroids are available in numerous formulations and whilst usually applied as either creams or ointments, they may also be delivered intra-lesionally via inhalers for eroded or mucosal surfaces, as lotions or foams, and also mixed with adhering agents such as orobase paste [37]. For calcineurin antagonists, the commercially available range of bases is more limited, with tacrolimus available as an ointment and pimecrolimus as a cream. These can also be mixed with paste such as orobase.

Local corticosteroid therapies can cause skin atrophy but have a much lower rate of other significant side effects and therefore, in our opinion, may contribute to reducing systemic immunosuppression. The largest study of topical therapies was conducted as a substudy of the STOPGAP study and recruited 66 patients who investigators felt had PG that would be amenable to local treatment [38]. The study was an observational prospective cohort study with no comparator group: 47 patients received clobetasol propionate 0.05%, 10 received tacrolimus ointment 0.1% and 8 received other treatments, mainly other topical steroids. At 6 months, 42% were completely healed with a median target lesion size of 4.4 cm^2 for the clobetasol group. The majority did not heal, suggesting that additional systemic therapy may have been beneficial.

3.2 Other Topical Options

The use of intra-lesional steroid injections for PG is widely reported in case reports and case series, often in the context of peristomal disease [39, 40]. It is important to consider the steroid strength. Triamcinolone is often used as it is relatively insoluble and therefore remains in the local area to a greater extent than dexamethasone. Based on our experience, we usually inject 1 ml of 40 mg/ml on the first visit around the edge of the ulcer. In subsequent visits every 4 weeks, we consider up to 2 ml of 10 mg/ml. Caution is needed with higher concentrations or injection volumes as skin atrophy is a common side effect.

A wide variety of other treatments have been reported. These include solutions or gels with cyclosporine, dapsone, methotrexate, cromolyn sodium solution, phenytoin solution, infliximab, etanercept, benzoyl peroxide, becaplermin and cannabis [41]. Topical timolol has been also described to be effective in promoting re-epithelisation in the wound-healing stage [42]. Future alternatives will most likely include topical Janus kinase (JAK) inhibitors such as tofacitinib or ruxolitinib [43]. Many of the reports are single case articles and none of these options are commonly used.

3.3 Considerations for Special Sites

Peristomal PG presents a significant diagnostic challenge and might be overdiagnosed [44]; important differential diagnoses such as toxic and allergic contact dermatitis must be ruled out [45]. However, the need for rapid control of inflammation necessitates therapy. Topical treatment alone may be considered in mild cases where the stoma apparatus is not affected, or in more severe cases as an adjuvant treatment to minimise systemic immunosuppression. The main problem with topical therapies in peristomal PG is the effect on the adherence of the stoma apparatus to the skin. Various solutions have been suggested; intralesional steroid is one option. Steroid lotions in an alcohol base such as super potent topical corticosteroids can work as the solution will dry quite quickly. Direct application of aerosol steroid from an inhaler has been reported [46]. Mixing ointments such as clobetasol 0.05% or tacrolimus 0.03% in oral paste can allow stoma adherence. Extra-thin hydrocolloid dressings have also been used to minimise trauma. A hole for the stoma is cut into a large sheet of hydrocolloid. Following the application of topical treatments, the hydrocolloid is stuck onto the skin with enough overlap onto normal skin. The stoma apparatus is then adhered to the hydrocolloid and a good seal can often be formed. New ostomy baseplates are also being developed to manage the problems of peristomal skin complications and may be beneficial in the management of peristomal PG [47]. Steroid impregnated tapes can be used and crushed oral prednisolone tablets mixed with stomahesive protective powder has been reported [48].

4 Systemic Treatments

While the main therapeutic options for classic PG remain those listed by Maronese et al. [49], evidence from a large, multi-centre, retrospective cohort study as well as an expert survey study shows that PG patients receive an average of two different systemic agents. This underscores the importance of combination treatments [50, 51] to achieve ulcer healing [2]. Combination treatment has not been defined but based on our experience, overlapping classic immunosuppressants and corticosteroid sparing agents for at least 4 weeks throughout the course of the disease is becoming standard of care in clinical practice when patient require systemic treatments (Table 3).

4.1 Classical Immunosuppressive Drugs

4.1.1 Systemic Corticosteroids

Corticosteroids are the first-line immunosuppressant for PG worldwide. They cause immunosuppression mainly

by sequestration of CD4+ T-lymphocytes in the reticuloendothelial system and by inhibiting the transcription of cytokines [52]. Treatment with systemic corticosteroids (CS) at a dosage of 0.5–1 mg/kg/day induces a clinical response in up to half of PG cases [53] but it has heterogeneous response rates [54]. Once healing has been reached, the CS dose can be tapered usually within 6 months [49, 50]; however, this decision should be guided by the clinician's experience and patient's input. Healing is achieved in approximately 40% of patients with multiple ulcers. It is recommended that systemic CS be combined with other immunosuppressants or immunomodulatory agents, the most common agent being cyclosporine [49]. Pulse therapy with 1 g of intravenous methylprednisolone for 3-5 consecutive days may also be considered in refractory cases [55, 56].

4.1.2 Cyclosporine

Cyclosporine is a calcineurin inhibitor that impairs the transcription of various cytokines, particularly in T-lymphocytes. A multi-centre, randomised controlled trial (Study of Treatments fOr Pyoderma GAngrenosum STOP GAP) compared oral prednisolone 0.75 mg/kg/day versus cyclosporine 4 mg/kg/day. There was no difference between the two treatments in terms of speed of healing over 6 weeks, time to healing, treatment response, inflammation resolution, pain, quality of life, treatment failures or time to recurrence. Of note, almost half of the patients healed within 6 months but almost a third of patients in both treatment groups had a recurrence after a median of 582 days. About two-thirds of patients experienced adverse effects in each group. The conclusion of the study was that the choice of prednisolone versus cyclosporine depends on patients' comorbidities, with cyclosporine being a more cost-effective choice in patients with large PG ulcers [57]. Pre-existing conditions favouring prednisolone over cyclosporine include renal insufficiency, malignancy and hypertension, whereas patients with obesity, diabetes, osteoporosis, peptic ulcer disease or a history of mental illness may benefit from using cyclosporine rather than prednisolone [58].

4.1.3 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug which inhibits T- and B-cell proliferation by blocking the production of guanosine nucleotides required for DNA synthesis. In one retrospective analysis of 26 patients, 85% of patients demonstrated clinical improvement, with 13 patients (50%) healing over 1 year. All patients were on concomitant prednisolone, and a considerable proportion were also on concurrent immunomodulatory and/or immunosuppressant medications [59]. Similar findings regarding

Table 3 Systemic agents with the highest level of evidence to treat pyoderma gangrenosum

	Administration	Level of evidence[b]
Classic immunosuppressants		
Prednisolone	PO	1B
Cyclosporine	PO, IV	1B
Biologics		
Infliximab[a]	IV	1B
Adalimumab[a]	SQ	2B
Canakinumab	SQ	2B
Secukinumab	SQ	2B
Vilobelimab	IV	2B
Ustekinumab	SQ, IV	3A
Classic immunosuppressants		
Mycophenolate mofetil	PO	2B
Immunomodulators		
Dapsone	PO	2B
IVIG	IV	3A

[a]US Boxed Warning: Patients treated with TNF-α inhibitors are at increased risk of developing serious infections that may lead to hospitalization or death. Most patient who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

[b]Level of evidence adapted from the Center for Evidence-Based Medicine (http://www.cebm.net): 1B individual randomized controlled trial; 2B: individual cohort study. Drugs with level of evidence 3 or less were not included in the table (methotrexate, azathioprine, tacrolimus, colchicine, IVIG, other biologics and small molecules).

efficacy, safety and tolerability of MMF have been documented in smaller case series and case reports, even in the setting of severe, tendon-exposing, refractory PG [60, 61] or if patients declined biologic treatment [62]. In a large single-centre study, mycophenolate sodium and mofetil were used in a considerable proportion of patients (75/118) and were associated with a lower rate of adverse events than cyclosporine. The same authors combined MMF with low dose cyclosporine in some cases [63].

4.2 Classical Immunomodulation Drugs

4.2.1 Dapsone

Dapsone is a sulfone with anti-inflammatory as well as antibacterial and antibiotic properties. In a retrospective series of 27 patients with PG, oral dapsone was used as an adjuvant in conjunction with either systemic, topical or intralesional therapies. CS were the most common concurrent therapy, followed by antibiotics, cyclosporine and TNF-α inhibitors. Despite the 96.9% response rate, with an average

time to initial response of 5.3 weeks, only 15.6% of patients achieved a complete response [64].

4.2.2 Intravenous Immunoglobulin

Intravenous immunoglobulin is (IVIG) a biologic agent made up of human antibodies. There are case reports, case series and systematic reviews on the treatment of PG with IVIG with doses from 0.5 to 2.0 g/kg [65, 66]. A systematic review evaluated 49 patients, reporting a healing in 53% or a partial healing in an additional 25% of patients. It should be noted that CS were additionally administered in 88% of patients [67]. In a retrospective study with 45 patients who had received IVIG in PG because of treatment resistance, 23 (51%) healed completely. When IVIG was added, patients with one ulcer were 4.1 times more likely to achieve complete healing than patients with more than one ulcer [68].

4.3 Biologics

4.3.1 Tumour Necrosis Factor (TNF)-α Inhibitors

A semi-systematic review found that 238 out of 356 (67%) patients had healed while on TNF-α inhibitors. Additionally, a review of published PG cases found 87% of patients eventually healed [69, 70]. Infliximab, adalimumab, etanercept, certolizumab pegol and golimumab have been successfully used in the treatment of PG; however, higher response rates favour adalimumab and infliximab. Response rates do not significantly vary by PG type or associated diseases, i.e. inflammatory bowel disease, haematological diseases, or other inflammatory disorders [69, 70]. To date, infliximab remains the only TNF-α inhibitor tested in a randomised, double-blind controlled trial [71] with a clinical benefit in 69% (20/29) of patients by week 6. In a phase III, open-label multi-centre study of 22 Japanese patients with refractory PG, adalimumab led to complete healing in 55% of participants by week 26 [72].

4.3.2 Interleukin (IL)-23 Inhibitors

In a semi-systematic review, ustekinumab proved effective in 71% of patients treated with this biologic [73]. In a case series, 68% (19/28) of patients treated with ustekinumab reported healing, including patients with all PG subtypes [74]. As IL-23 is implicated in the pathogenesis of PG and associated inflammatory comorbidities, newer IL-23 inhibitors targeting the p19 subunit are now being also used in the treatment of PG [75, 76].

4.3.3 Interleukin (IL)-1 Inhibitors

The IL-1 inhibitors used for the treatment of PG include anakinra (IL-1 receptor antagonist that blocks IL-1α and IL-1β) and canakinumab (IL-1β inhibitor). The latter being the only IL-1 inhibitor tested in a phase 2 open label trial [77] in which three out of five patients were completed healed by week 16. Adding reported cases of PG treated with canakinumab, 6 out of 11 patients reported complete healing and clinical improvement in 1 of 11 [73]. On the other hand, anakinra showed significant clinical improvement or complete remission in 10 of 13 patients [70]. These biologics have been particularly beneficial in patients with autosomal dominant autoinflammatory syndromes such as pyogenic arthritis, PG, acne (PAPA) spectrum disorder [78].

4.3.4 Interleukin (IL)-17 Inhibitors

Sparse reports have described successful PG treatment with interleukin IL-17 inhibitors, including secukinumab (anti-IL-17A) [79], brodalumab (anti-IL-17 receptor) [80] and ixekizumab (anti-IL-17A/F) [81]. An open-label phase II trial evaluated the efficacy and safety of secukinumab monotherapy in treating PG. Although three out of seven patients worsened, the others reported pain reduction, with two experiencing clinical improvement and reduction in inflammatory markers [82]. Brodalumab either weekly or biweekly led to clinical improvements in three patients [80]. On the other hand, IL-17 inhibition has induced PG [83, 84], most likely due to paradoxical IL-23 upregulation [85]. PG induction has also been documented upon switching between anti-IL-17 agents [86].

4.3.5 Complement Factor C5a Inhibitor

Vilobelimab (IFX-1) is a chimeric monoclonal antibody that inhibits neutrophil activation, chemotaxis, reduces inflammatory signalling and complement driven tissue damage in various diseases such as hidradenitis suppurativa [87, 88]. A phase IIa open-label study testing the efficacy and safety of IFX-1 in patients with PG (NCT03971643) is now finished. A total of 19 patients were enrolled in the study. Seven patients were in the dosing cohort at 2400 mg intravenous biweekly; six of these seven patients were healed by the end of the study (ClinicalTrials.gov).

4.4 Other Systemic Therapies

Of the currently available other systemic therapies, small molecules seem to be the next most promising therapeutic alternative for PG [89–91]. However, there are only a few case reports and further studies are required.

5 Adjunctive Management

5.1 Wound Management

The principles of modern moist wound therapy also apply to PG. However, due to the pronounced inflammation and painfulness, special consideration is required for certain aspects of wound care in PG. First, surgical debridement should not be performed during the inflammatory phase due to the pathergy phenomenon. Here, atraumatic alternatives such as maggot therapy or autolytic (e.g. hydrogel) or enzymatic (e.g. collagenase) may be considered [92]. Because the risk of wound infection is higher in patients receiving systemic immunosuppression, we believe that the use of antimicrobial dressings, for example polihexanide- or silver-containing wound products, is reasonable [93]. Non-adhesive and hyperabsorbent wound dressings are an important aspect of this strategy as adequate exudate management must be ensured [94].

When PG occurs on the lower legs, compression bandages should be applied to support anti-inflammatory activity by reducing oedema [95]. In our experience, low resting pressures around 20 mmHg are sufficient and better tolerated [96].

5.2 Pain Management

It has been demonstrated that a PG significantly limits patients' quality of life, mental health and ability to work [97, 98]. Domains to specifically assess the impact of PG have been established, one of which is pain [99]. Pain remains an important aspect to take into consideration when addressing the severity of PG [100]. Several instruments have been used to assess quality of life including pain, though there none are specific to PG. Improvement in pain scores by at least two points in a numeric rating scale (0–10) might be an early sign of healing and seems to be an accurate patient-reported outcome to assess the disease impact and response to therapy [101].

6 Treatment Algorithm

From our experience, local pharmacologic therapy only can be attempted when there are single small (≤ 4 cm^2) PG skin lesions with or without ulceration. The most common approach is to use a high potency steroid (e.g. clobetasol) or a calcineurin inhibitor (e.g. tacrolimus). In a comparative prospective study of these two alternatives, ulcer size was an independent predictor of healing [38]. When using topical therapy for PG, it is important to closely monitor progress with objective measurements and photography, in addition to establishing a strict timeline for re-assessment of therapy. The addition of systemic treatment should be considered if progress is lacking after 2–4 weeks of therapy. In addition, given the prolonged duration needed to control the inflammation, treating PG with local therapy can contribute to bridging or tapering the systemic immunosuppression and decrease the possibility of side effects. In general, topical therapy for PG is used as an adjuvant to systemic therapy and is usually applied to the ulcer itself and/or ulcer edges [41].

Systemic therapy should be considered when an ulcer is large (> 4 cm^2) or if there are numerous or PG ulcers. CS and/or cyclosporine have been used for many years due to their rapid onset of action in stopping and/or decreasing the progression of skin ulcerations. However, the healing rate is less than 50% at 6 months and classical side effects associated with each type of medication determine which patient might benefit from one or the other. Sparing agents are often added to first-line immunosuppressive medications to maintain the inhibition of the immune system. Currently, the most commonly used sparing agents are biologics. Most the data, including one randomised control trial (RCT), favours the use of TNF-α inhibitors, particularly infliximab. However, growing evidence has shown that inhibitors of IL-1, IL-12/23, IL-17 and C5a are another alternative to be considered (Fig. 3).

Biologics can already be used as first choice drugs in patients with inflammatory comorbidities such as IBD and inflammatory arthritis. Here, approval exists and several disease aspects can be treated simultaneously with one therapeutic agent.

In paraneoplastic PG, there is stronger evidence that treatment of the underlying malignancy may be helpful in treating PG. This does not always preclude the initiation of systemic immunosuppression as initial treatment when it is first required. Nevertheless, immunomodulatory therapy with options such as dapsone or IVIG can be considered initially.

It is always difficult to determine when systemic therapy should be stopped. It is important to remember that systemic therapy is intended to control inflammation. If no more inflammation can be detected, then systemic therapy can be successively reduced and does not necessarily have to be continued until the wounds are completely healed. However, this decision must always be made on an individual basis.
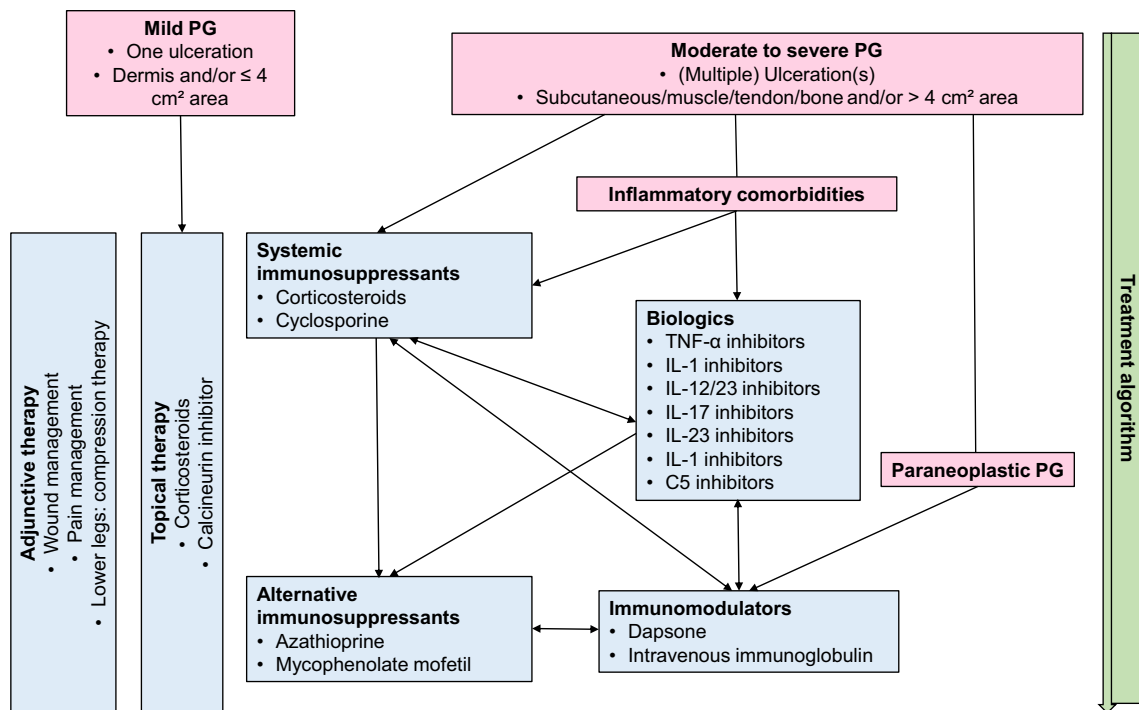
Figure 3 Algorithm of treatment options for pyoderma gangrenosum. *PO* per oral, *SQ* subcutaneous, *IV* intravenous, *IVIG* intravenous immunoglobulin.

7 Discussion

The clinical picture of PG was first described by Brocq over a hundred years ago [102]. It is still an enigmatic disease for healthcare providers and even more so for patients who often endure consultation with many physicians prior to finding one who might be familiar with the diagnosis and treatment of PG and able to provide much needed care and comfort. Sustaining progress in the management of PG relies on understanding its pathogenesis. It is still not known what stimulates neutrophil trafficking to cause skin ulcerations. It seems that abnormal activation of the innate immune system in patients with genetic predisposition provide an ideal state for PG to develop [103]. However, neutrophil-T cell cross-talk causing the activation of Th17 downstream cytokines is now supported by gene expression studies [6, 104].

Systemic therapies with CS and cyclosporine have remained the first-line options for most PG patients for several years. Despite the increased use of biologic therapy and the association of PG with inflammatory comorbidities, there is still a lack of strong evidence in support of their acceptance by regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [49]. If these patients do not have an associated comorbidity, the approval of biologics in clinical practice is even more challenging. The current evidence for the use of other, non-biologics favours MMF and dapsone (Table 3). These can be used as sparing agents, but their onset of action seems to be slower. However, the use of dapsone might confer Pneumocystis jirovecii prophylaxis (PJP) in patients treated with immunosuppressive for longer periods of time [105]. In addition, the appearance of PG ulcers on more sensitive areas (face and neck, genitalia) or the association with extracutaneous manifestations (e.g. lung involvement) might prompt the consideration of more aggressive initial treatment which could include pulses of CS or combination of CS with cyclosporine.

With all forms of therapy, it is very important to clarify in advance whether these treatments are at all feasible for patients who often have underlying illnesses. This involves clarifying side effects, but also the type of therapy to be carried out and whether the implicit costs will be covered by the insurer. Especially in the inflammatory phase, patients must be monitored closely. With control of the inflammation, the pain should decrease and the livid border around the wound should recede. If clinical symptoms progress despite 2–4 weeks of therapy, therapy should be extended or changed. Moreover, in the event of unsuccessful therapy, the PG diagnosis should also be critically questioned and, if necessary, re-examined. Misdiagnosis is still the main issue with PG [8]. Despite the proposal of new diagnostic frameworks, the impact on the misdiagnosis rate is yet to be seen.

As clinical guidelines are in development, healthcare providers rely on their knowledge of PG pathophysiology combined with their experience in wound care principles and training in analgaesic strategies to determine the most appropriate approach to treat these patients. Although more and more drugs are available for the medical treatment of PG, most are still considered off label and access is an issue for patients worldwide. When patient does not respond appropriately to immunosuppressive therapy, misdiagnosis is a consideration. However superimposed cellulitis or other concomitant ulcer aetiologies (e.g. chronic venous insufficiency) have to be addressed to assure treatment response. Conversely, high doses or levels of immunosuppressants can also negatively affect healing throughout the course of the disease.

In the future, we need to deepen our understanding of the pathophysiology of this disease, search for specific markers to aid in the enrolment of patients in clinical studies and possibly to distinguish PG from other ulcerative skin diseases, and ultimately develop targeted therapies that can feasible be studied in RCTs.

8 Conclusions

PG is a rare inflammatory dermatological disease that leads to very painful ulcerations and causes a significantly reduced quality of life. Once the diagnosis is confirmed with validated scores, numerous immunosuppressive and immunomodulatory therapies are now available. In particular, biologics will play an increasingly important role in the treatment regimens of patients with PG.

Declarations

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