REVIEW ARTICLE

CURRENT AND EMERGING TRENDS IN THE MANAGEMENT OF PYODERMA GANGRENOSUM: A LITERATURE REVIEW

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The first description of Pyoderma gangrenosum (PG) was made about a century ago. It is difficult to understand the aetiology, pathophysiology, and therapy of PG. This disease is believed to be caused by a systemic inflammatory response to neutrophil chemotaxis and faulty innate immune system control. Nearly fifty percent of the cases have underlying systemic symptoms. Significant improvements in PG management have been made over the years. The main goals of treatment are to reduce inflammation and speed up the healing of the PG wound. Even though the most recent medicines show promise, they are found on isolated case reports. The majority of patients are typically managed with topical treatment and local wound care, while resistant cases necessitate immunosuppressive medications. More progress can be made with improvements in technology in deciphering this complex disease and getting a greater understanding of the condition. The present standard therapies for refractory PG are not well supported by studies. In refractory PG, corticosteroids and cyclosporine have historically been administered. Tumour necrosis factor inhibitors are becoming a viable option; nonetheless, this requires careful research and upkeep.
This review intended to describe the current trends in managing the PG. Several next-generation treatment options including the conventional therapies introduced to treat PG. We encompass the advantages and disadvantages of new treatments for PG.

Keywords: Pyoderma gangrenosum; Systemic management; Refractory; Immunosuppressive

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INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, painful, non-infectious ulcer, with indistinct aetiology. The hallmark of PG lesions is necrosis at the base of an excruciatingly painful ulcer and an undermined border encircled by an increasing zone of erythema.[1] The disease usually presents in conjunction with other conditions including inflammatory bowel disease (IBD), arthritis, and other inflammatory disorders. PG is commonly manifested as ulcer, pustular, bullous, vegetative, or superficial granulomatous along with some rare clinical presentations. PG is a widespread disease. Previous studies indicated that the estimated incidence ranged from 3 to 10 cases per million per year.[2] No age group is immune to the effects of PG, which typically affects persons between the ages of 20 and 50, with a female predominance.[2] The pathogenesis of PG is unknown; however, it is thought to entail dysregulation of the adaptive and innate immune systems, neutrophilic abnormalities, aberrant phagocytosis, and genetics.[3–6] There are no validated criteria for the diagnosis of this disease. Nevertheless, diagnosis is based primarily on clinical symptoms and the course of disease in individual patients. Multiple baseline clinical investigations are required to conclude a diagnosis of PG along with ruling out underlying systemic involvement as shown in Figure 1.

In refractory patients, the most commonly utilized therapies in PG are ineffective.[7] The use of biologics in PG has expanded as a result of the great strides in the treatment of inflammatory diseases in recent years.[8,9] Together, these most recent studies offer invaluable insights into the treatment of inflammatory illnesses. Until now different therapeutic modalities, including local and systemic treatments, have been utilized to cater to PG to impede disease progression, support re-epithelization, and reduce scarring.

The aggressive nature of this disease hinders universal treatment modality options. Moreover, targeting the systemic-associated disease also results in reduced symptoms of PG. Several treatment modalities have been introduced by different clinicians around the globe to manage PG. These include the standard, systemic, and next-generation treatment strategies. This review article aimed to encompass the conventional and latest treatment options for the management of PG.

Management of PG

Different treatment options used for the management of PG are summarized in Figure 2. Here, a brief overview of these treatment options is narrated:

Standard Management Options

Topical and Intralesional Corticosteroid

Topical corticosteroids are usually thought to be less effective in repairing PG lesions, except for a few positive outcomes.[10] They act in the healing process for wounds, inflammation, proliferation, and remodelling.[11] Betamethasone 17 valerate 0.1% lotion was used to treat a case of PG that spread to the scalp, resulting in complete healing.[10] In retrospective research, Amy *et al*. examined 7 cases of PG with various underlying systemic diseases. The results showed that topical and intralesional highly powerful corticosteroids were effective in 2 of 7 patients. Together with topical corticosteroids, these individuals also received systemic therapy.[12] As a result, there is insufficient data available to determine whether topical steroids are effective in treating PG.

A better response to intralesional corticosteroid therapy is shown in the early lesion of PG.[10] In addition to systemic steroids, an intralesional triamcinolone acetonide (Kenalog 40 mg) injection was used to treat PG lesions. The patients responded favourably to the treatment, and follow-up examinations revealed no recurrence.[13] In another instance, 0.5ml to 1.0ml of intralesional triamcinolone acetonide proved effective in PG lesions with chronic hepatitis.[14] Thus, an intralesional corticosteroid may be used as a substitute therapy for early PG lesions. The effectiveness of intralesional steroids as a PG adjunctive treatment has been emphasized in several case studies.

Tacrolimus

Tacrolimus, isolated from *Streptomyces tsukubaensis*, is a hydrophobic macrolide immunosuppressive agent and hinders the expression of both IL-8 and IL-8R in keratinocytes.[15] Tacrolimus complex type and FKBP, or the binding protein, were initially given the nomenclature FK506. Tacrolimus is an example of an immunosuppressive medication described as adjuvant therapy for PG in addition to systemic treatment.[16] Topical tacrolimus can be used on its own and as a supplement in cases where systemic immunosuppressive drugs are constrained by adverse effects and associated diseases.[17] However, infections and cancer are two potential side effects of tacrolimus.[18] It is important to perform more research to evaluate topical tacrolimus therapy in PG.

Sodium Cromoglycate

As PG exhibits an aberrant immune response, Sodium Cromoglycate (SC) is thought to work by causing mast cells to release histamine through an allergic mechanism, which can happen similarly to bronchial asthma. The impact of topical 1% SC was demonstrated in 5 patients with pyoderma gangrenosum. The patients showed recovery either when SC was being used alone or as an adjuvant.[19] Likewise, A woman with a history of both PG and UC was reported to have a partially healed ulcer after two years of treatment with Sulphasalazine and prednisone. Therefore, topical disodium cromoglycate was added to the treatment regimen for PG. The PG ulcer completely recovered as a result.[20]. Similar results were also reported by Cock *et al* in 1979.[21]

5-aminosalicylic acid

Topical 5-aminosalicylic acid is a known topical treatment for IBD, which has been shown to reduce tissue corrosiveness and inflammation.[10] A female patient with PG and CD was given 10% topical aminosalicylic acid treatment every day. After five weeks, there was a notable clinical improvement. However, the CD symptoms remained unaltered and further studies are required to assess the effectiveness of the acid in treating PG.[22]

Topical nitrogen mustard

It is an alkylating agent with an unclear mechanism of action. However, this is a frequent choice in cancer therapy due to its immunosuppressive and anti-inflammatory characteristics.[23] A male patient with a PG lesion was treated successfully with 20% nitrogen mustard and plasmapheresis after three months of treatment.[24] Further research is necessary to ascertain the safety and effectiveness of nitrogen mustard in PG.

Benzoyl peroxide

Topical benzoyl peroxide 20% was reported to successfully treat a case of PG ulcer in six weeks.[25] A case of subacute PG was completely treated with topical benzoyl peroxide and stabilized with lymecycline and autograft.[26] While benzoyl peroxide is not proven effective in the treatment of PG, additional studies are required to substantiate the aforementioned findings.

Topical nicotine

Nicotine reduces inflammation by having an impact on immune cells, the peripheral and central neurological systems, and the endocrine system.[27] In a case study, a male patient with a PG lesion connected to non-granulomatous colitis showed significant improvement when treated with topical nicotine daily for 3 months.[28] The effects of nicotine are currently unclear based on a small number of studies, but the effectiveness and safety of nicotine can only be determined through randomized clinical trials.

Platelet-derived growth factor (PDGF)

PDGF is derived from the alpha granules of the platelets and acts as a key mediator of abnormal cell growth and a regulator of cell proliferation.[29] Falco *et al*. reported a 52-year-old man with a growing PG ulceration on the dorsal portion of his right hand due

to Myelodysplastic Syndrome (MDS). He was treated with topical PDGF therapy and systemic corticosteroid therapy, leading to a noticeable improvement. The use of PDGF as an adjuvant therapy in conjunction with systemic therapy may hasten the healing of the PG wound.[30] Further research with sufficient follow-up is required to evaluate the effectiveness and safety of PDGF.

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

The hematopoietic growth factor, which is a significant component of GM-CSF, is what gives mature functioning macrophages their characteristics.[31] In a case report, Lucile *et al*. described a 23-year-old male patient who had Hodgkin's disease. Together with chemotherapy drugs like vinblastine, bleomycin, and dacarbazine, he received prophylactic GM-CSF. It was challenging to rule out chemotherapy's role in the PG lesion's emergence. Intravenous immunoglobulin IVIg was also provided which revealed disappointing outcomes, further followed by prednisone with clinical improvements. Prednisone may be the reason for the favourable findings, while GM-CSF may not be effective in patients with PG, which could explain the discrepant outcome.[32]

Systemic Treatment Options

PG has been effectively treated with corticosteroids. However, the side effects of these steroids forced clinicians to look into other immunosuppressive agents with the lack of steroidal effects for the systemic management of this disease.[33]

Corticosteroid

Systemic corticosteroids are used as the first line of treatment for PG with acute, rapid progression. The necessary maintenance dose varies significantly from 40–120mg.[10] In a rare PG case with organ involvement, Lebbe *et al*. found rapid and significant improvement in pulmonary and skin lesions following therapy, but with a risk of recurrence after dosage reduction.[34] Corticosteroids are not specific, and the most significant limitation is the variety of side effects associated with long-term corticosteroid use. Recalcitrant PG can be treated with intravenous high-dose pulse steroid therapy, but there is a risk of arrhythmias and electrolyte shifts.[23] As a result, the majority of patients experience corticosteroid-induced complications while on therapy.

Cyclosporine

Cyclosporine was first developed in 1972 from the fungus *Tolypocladium inflatum.* Due to its potent immunosuppressant properties, it was initially utilized in organ transplant patients. Cyclosporine inhibits T cells' release of lymphokines particularly interleukin 2.[35] In a case series of 11 patients with resistant PG, low-dose cyclosporine completely cleared the PG ulcers. These results influence the authors to report that Cyclosporine should be used as the first line of treatment for PG lesions.[36] Similarly, successful clinical improvement of PG lesions using prednisone and low-dose cyclosporine (7.5 mg/kg/day) was reported in a study.[37] These studies suggest that cyclosporine's effects on PG may be beneficial and safe.

Cyclophosphamide

Cyclophosphamide is an alkylating substance with cytotoxic and immunosuppressive effects.[38] It was found to be beneficial for patients with recurrent progressive PG without systemic involvement.[39] Stanley *et al* reported a case of a girl who developed PG as a side effect of penicillin injection which was resistant to antibiotic medication and local wound care. Cyclophosphamide and prednisone were administered for three months. After six months of medication, the PG lesion completely disappeared due to the gradual reduction of the steroid dosage. Following the administration of cyclophosphamide, leukopenia, and hair loss were seen.[40] According to these findings, more research is needed to prove the effectiveness of cyclophosphamide in the treatment of PG.

Methotrexate

It was once thought that the cytotoxic drug methotrexate worked by preventing the formation of purines and pyrimidines. Moreover, it was demonstrated that it might also function as a chemotherapeutic drug.[41] Teitel *et al*. described the successful control of PG with methotrexate in a patient who was unresponsive to topical medicine, skin graft, and immunosuppressive therapy. Interestingly, a rapid response to treatment was observed once a course of methotrexate in conjunction with steroids was started. According to the author, methotrexate may function by preventing neutrophil migration and chemotaxis in light of the findings of neutrophil dysregulation in the pathophysiology of PG.[42]

Dapsone

Dapsone is used to treat a variety of skin problems. Oral dapsone was reported to be used in bilateral PG of the hand by Brown *et al*. One lesion initially exhibited clinical improvement after receiving two months of local wound treatment. After a prior lesion on the contralateral side healed, a new lesion quickly developed. Regression was shown four to six weeks after beginning oral treatment. The author claimed that dapsone may function by preventing the necrotizing process and aiding in the development of early epithelialization.[43]

Thalidomide

Thalidomide was initially used as a sedative and an antiemetic until its ban for teratogenic effects. Thalidomide is thought to have anti-inflammatory and

immunomodulatory properties. After noticing its outstanding impact, this medication was reintroduced for the treatment of erythema nodosum and other disorders.[44] Federman *et al* used the case of a man with confirmed PG who failed to respond to numerous doses of steroids as an example. When the patient's thalidomide therapy was initiated, the PG ulcer significantly regressed.[45] Thalidomide should be taken into account in PG instances that are refractory.

Clofazimine

Clofazimine has anti-inflammatory properties and is used to treat refractory leprosy and tuberculosis with a usual oral dose of 100 mg/day. Ten patients with PG who also had systemic disorders were investigated by Thomsen *et al*. and were given 100 mg of clofazimine three times a day. Clofazimine improved the PG lesion in seven patients, with three cases showing partial improvement.[46] In another study, eight patients were treated with clofazimine, which exhibited a positive clinical response with rapid regression within two weeks of treatment. The author concluded that the precise mechanism of clofazimine's activity in PG is yet unknown.[47]

Tacrolimus

Tacrolimus is a well-known macrolide that blocks CD4 helper T lymphocytes. A patient with PG was given 0.15 mg/kg tacrolimus FK 506 twice a day in a report by Elmaged *et al*. After 12 weeks of therapy, the issue was fully resolved.[48] In another instance, low-dose tacrolimus was found to be effective in combination therapy with steroids in PG resistant to other systemic modalities. The patient did, however, experience a tingling sensation in extended limbs.[49] The limited and sparse nature of these studies does not support tacrolimus being used as an alternative for PG treatment.

Azathioprine

Azathioprine is a cytotoxic medication that can be used alone for 2–4 weeks or in conjunction with steroids at a dose of 100–150 mg/day. Nonetheless, it is important to perform routine examinations of the transaminase and complete blood count.[50] It was reported that idiopathic PG patients with compromised cellular immunity should not receive long-term immunosuppressive medications.[51] To achieve safe management, careful patient selection and thorough monitoring must be used. It is important to conduct controlled prospective studies to assess the effectiveness and tolerability of azathioprine in people with idiopathic PG.

Minocycline

Antimicrobial medication minocycline, when taken daily in doses of 200–300mg, is also beneficial in PG. In terms of this medication's effectiveness in reducing inflammation, tetracycline is a close relative.[50] Minocycline produces a safe and effective response in the treatment of recalcitrant PG.[52] To validate these results, however, large-scale randomized controlled trials are required.

Chlorambucil

As a slow-acting alkylating agent than cyclophosphamide, this medication is less harmful.[10] Six cases with refractory PG were investigated and results showed that all six individuals did not respond to immunosuppressive medication, such as corticosteroids. Oral chlorambucil was begun at doses of 2–4 mg/day for these patients. All patients saw positive clinical outcomes within 6–8 weeks but then weaned off until they were completely stopped. Relapse happened in two patients four months after the end of their therapy, with one patient having leukopenia. Chlorambucil was recommended by the author as a helpful treatment for severe PG.[53]

Cyproheptadine

Cyproheptadine possesses properties that degrade platelets. It functions as an antiserotonergic agent and histamine inhibitor. It has been noted in earlier studies of PG linked to UC that it aids in endothelial proliferation, particularly in small blood vessels.[10] Cyproheptadine showed promising results in 10 days in two cases of PG along with UC with pain relief within 12 hours of administration.[54] The only downside is that there are no additional reports of cyproheptadine in the treatment of PG.

Skingraft

Cliff *et al*. found that split skin grafts are an effective treatment for traditional PG. To limit the pathergy process, it is advisable to start immunosuppressive therapy at first followed by continuing treatment for an extended duration. It is important to take into account the dose and duration of an immunosuppressant that will be effective in maintaining the clinical improvement of the PG lesion. According to this research, skin split graft therapy can help treat PG coupled with immunosuppressive therapy.[55]

New Management Options

Local Wound Care

To effectively treat early localized lesions of PG, local wound care is crucial. The following list includes some dressings that have been applied to chronic or exudative lesions:

1. In the treatment of chronic lesions, moisture-retentive dressings outperform desiccative gauzes in terms of pain management and wound healing.
2. In exudative wounds, alginates are a crucial substitute for occlusive dressings.[56]
3. Barrier cream, such as zinc oxide paste, aids in stopping future skin deterioration.[57]
4. Covering the lesion with layers of gauze soaked in petrolatum can help prevent local harm to the ulcer.[57]

5. Topical antibiotics like metronidazole and mupirocin can be administered.[10]

Depending on how the PG lesion appears, wound treatment may be given. Resistance to microorganisms may develop as a result of antimicrobial use. Contact dermatitis can be brought on by neomycin. Acetic acid soaks can decrease the growth of pseudomonas.[23]

Topical Treatment

Laurence LE Cleach treated localized PG with a topical corticosteroid, clobetasol propionate 0.05% ointment, topical tacrolimus 0.1%, and oral medication. With this therapy, the lesion nearly entirely vanished, and only minor side effects, such as a burning feeling, were noticed after the course of treatment. The lesion was completely healed within two weeks. However, the lesion reoccurred seven months post-treatment and was once again treated with 0.1% tacrolimus ointment.[58] To support these conclusions, additional research examining this strategy in localized PG is needed. Adding to this, there is a serious lack of trials concerning other topical therapies except for corticosteroids and calcineurin inhibitors.

Topical phenytoin sodium

Topical phenytoin works by causing fibroblasts to proliferate, granulation tissue to develop, and collagen to be deposited. Patients with resistance to systemic therapy were given a topical 2% phenytoin sodium solution in addition to the systemic therapy, resulting in two patients healing with partial resolution and four responding to therapy with exceptional results.[59] For challenging instances, topical phenytoin may be investigated as an alternate source.

Pimecrolimus 1% cream

Systemic corticosteroids and topical 5-aminosalicylate were used to successfully treat recalcitrant PG associated with UC. However, at recurrence, the patient received pimecrolimus cream 1% twice a day in addition to prednisone treatment. After two weeks, the PG lesion started to gradually heal, and after 12 weeks of combined therapy, the lesion was completely gone. At the 12-month follow-up, no recurrence was found.[60] Since systemic therapy alone cannot be used to treat severe instances due to side effects, a larger sample of patients should get this technique in future research.

Tacrolimus

The earlier study on topical tacrolimus therapy for PG was supported in 2006 by the report of Angelo and colleagues.[61,62] Topical and intralesional steroid therapy failed to help a 56-year-old female with PG ulceration, but the local application of topical tacrolimus led to impressive healing. This result corroborated the earlier research and suggested that topical tacrolimus might be effective in reducing systemic medication and improving the prognosis of localized PG lesions.

Negative Pressure Wound Therapy (NPWT)

A crucial role in pain management in PG is played by negative pressure wound therapy (NPWT), which uses gauze. This role may be explained by the different types of foam-based approaches used, in which the formation of granulation tissue occurs deep within the foam's micropores. This approach requires fewer dressing changes regularly. NPWT effectiveness was demonstrated in four patients who were on multiple systemic immunosuppressive medications. The study illustrates the efficacy of granulation tissue stimulation using gauze-based NPWT. Moreover, it aids with PG pain reduction and wound care.[63] To assess the efficacy of NPWT in healing[56], local wound healing and pain reduction in conjunction with systemic therapy, additional clinical trials on large samples are required.

Beclomethasone inhaler

Chriba *et al* used the example of a male patient who had Crohn's Disease and peristomal PG for four months. The patient had undergone ileocaecal resection and an ileostomy. Within one month of treatment, a change was shown after using a beclomethasone dipropionate 200 µg inhaler four times/day. Although intralesional steroid injection in peristomal PG is typically a painful technique, there were no adverse reactions reported. The author asserted that the use of steroid spray is beneficial in peristomal ulceration of PG even though topical steroid creams or ointments had been administered with no improvement in the lesion.[64]

Swedish Snuff Therapy

Kluger *et al* found that Swedish oral-type moist snuff could be beneficial in localized PG lesions. However, it is uncertain whether patients with idiopathic PG or systemic disease-related PG should be given a nicotine substitution or snus (snuff).[65] Further case-control studies with matched controls and lesser snus (snuff) use should be conducted to evaluate the possible efficacy of snus in PG and healthy controls.

Biologic Interventions

The use of specific types of biologics has been the subject of encouraging reports in the scientific review. By targeting the action of proinflammatory cytokines using medications like infliximab, adalimumab, and etanercept, anti-TNF alpha is helpful in the inflammatory response in a variety of disorders. Due to an apparent response in extraintestinal disorders like PG, anti-TNF alpha therapy is a newly available therapeutic option in challenging IBD cases. As a result, it is viewed as a treatment option in PG cases that are refractory, particularly when PG is linked to intestinal disease.[66,67]

Infliximab

Infliximab is a chimeric anti-TNF monoclonal antibody (IgG1) that binds to monomeric, dimeric, and trimeric TNF alpha, preventing TNF-alpha from interacting with its receptor and inducing apoptosis in cells.[68] Infliximab has been an effective treatment option for refractory PG. In a double-blind, randomized, placebo-controlled clinical trial conducted by Brooklyn and colleagues 30 patients who were older than 18 years old were given a placebo and infliximab at 5 mg/kg at 0 and 17 weeks. After two weeks of medication, 46% of patients had clinical improvement, compared to 6% improvement in the placebo group. Infliximab was found to be a more effective treatment option than the placebo group as it showed encouraging results in clinical response.[69]

As per retrospective results of a study, Infliximab was used to treat 13 patients with moderate to severe PG associated with IBD. Three patients showed excellent clinical response, requiring no further treatment. It is a safe and effective treatment for PG related to IBD, but it is costly and risky.[70] To achieve safe management, careful patient selection and thorough monitoring must be used.

Adalimumab

A completely human monoclonal IgG1 antibody that targets TNF-alpha is called adalimumab. It is mostly used to treat autoimmune diseases including rheumatoid arthritis. The suggested dosage is 40 mg subcutaneously every other week, but some patients might require weekly administration.[71]

In one report, Adalimumab therapy gave a remarkable clinical improvement in PG combined with IBD. The patient had been refractive to all other types of PG management modalities including infliximab, azathioprine, oral antibiotics, IVIG, and standard topical treatments.[72]

Another study reported a patient with PG along with multiple co-morbidities including diabetes, osteoarthritis, and hypertension. Adalimumab was suggested as a substitute treatment option for those patients whose illness condition may be worse by other immunosuppressive medications and other risk factors. Adalimumab was administered along with Unna wraps and topical clobetasol 0.05% ointment. After 5.5 months of this therapy, clinical improvement was observed. Thus, in severe PG that is refractory to conventional therapy, adalimumab can be utilized as an alternate therapy.[73]

Etanercept

Etanercept was the first drug the FDA licensed for the treatment of psoriatic arthritis.[74] Etanercept binds to soluble TNF alpha more strongly than infliximab does, and it forms a less durable binding complex with monomeric TNF alpha and membrane-bound TNF alpha.[75]

According to the Pastor and group, Etanercept showed good clinical results in a patient with a PG ulcer who was formerly managed by cyclosporine and prednisone in only 8 weeks.[76] In their case report, Goldenberg *et al*. showed how etanercept helped a patient with autoimmune liver disease who had unique bilateral PG ulcers on their extremities resistant to standard treatments. Following the introduction of etanercept and the tapering of prednisone, clinical improvement was seen.[77] Charles and the team performed a retrospective analysis to assess the safety and effectiveness of subcutaneous Etanercept in seven patients. All patients showed improvement, except for one patient who had faced multiple side effects.[78]

Alefacept

A recombinant protein called alefacept blocks the LFA-3/CD2 interaction, which interferes with T-lymphocyte activation and changes the inflammatory response.[79] It is used as an approved treatment for plaque psoriasis. A drop in CD4 T cells is seen after alefacept medication, and this should be watched for both before and after treatment every week. Therapy should be terminated if the CD4 count falls below 250 cells/micro L for a month.[80] There are no known side effects of alefacept. According to a pilot study, Alefacept may be a viable alternative to other treatments for PG ulcers that are not responding.[81]

Efalizumab

The monoclonal antibody efalizumab, which has been fully humanized, binds to the CD 11a small unit of the leukocyte function associated antigen type (LFA -1). LFA-1 mediates leukocyte adhesion and migration. In a case report of a patient with persistent pyoderma gangrenosum after 6 months of treatment, Woodson *et al* demonstrated complete remission of PG. It has now been discontinued for use.[80,82]

Visilizumab

It is a humanized IgG2 monoclonal antibody. It stimulates the synthesis of particular chemokines and reduces the CXCR3-linked chemotaxis of dormant lymphocytes in peripheral blood. Visilizumab causes quickly occurring apoptosis in activated T lymphocytes.[83] Lorincz M *et al*. published a case report of a 40-year-old male patient who experienced 30 different therapy courses due to misdiagnosis for various dermatological disorders. He participated in a visilizumab study for his condition. After six months of intravenous therapy,

the PG lesion showed a significant improvement, with no undesired outcomes.[84]

Interleukin-23 expression and ustekinumab

Guenova and associates examined tissue samples where high transcriptional and protein levels with higher IL-23 expression in refractory PG were discovered. Ustekinumab, a medication that targets the p40 component of IL-23, was launched as a treatment as a result of this mechanism of action. After 14 weeks of therapy, significant clinical improvement and a decline in IL-23 expression in refractory PG were seen. The study emphasizes the existence of an inflammatory infiltrate with a predominance of IL-23 in resistant PG. This observation leads to the assumption that PG and IBD share a common pathogenic mechanism.[85]

Mycophenolate mofetil (MMF)

Mycophenolic acid's prodrug, MMF, inhibits inosine monophosphate dehydrogenase. This enzyme limits the rate of guanosine nucleotide production.[86] An 18-year-old female with long-standing peristomal PG was reported by Jeffery and a colleague in 2004. She experienced side effects from all other modalities. Ultimately, tacrolimus 0.1% topical ointment for local wound treatment was started along with MMF 1gm twice daily. After one month of MMF administration, mild healing was seen, and after five months of therapy, a full resolution was attained. There was no ill-effect noted. These results suggest that MMF might be an effective and secure treatment for peristomal PG.[87]

Intravenous Immunoglobulin (IVIG)

Ten individuals who presented with refractory PG were investigated by Cummins *et al*. For a month, 2 g/kg of IVIG was given, evenly distributed over 3 days. Five of the ten patients who had IVIG treatment suffered nausea and headaches, while seven of the ten patients experienced a complete clinical response. Current research has demonstrated the value of IVIG as an expensive supplementary therapy for refractory PG patients who are unable to tolerate the side effects of immunosuppressive drugs.[88]

Oral potassium iodide

A patient with a disseminated PG lesion was treated with oral potassium iodide, according to a case study by Li Qiu *et al.*[89] This lesion was resistant to dapsone, thalidomide, and minocycline and displayed oral prednisone dependence. Potassium iodide monotherapy showed clinical improvement in the PG lesion. There were few negative consequences found. In the current situation, potassium iodide therapy may be viewed as an experimental strategy in circumstances where conventional treatment has failed.

Granulocyte apheresis (Adacolumn)

The extracorporeal apheresis technique known as granulocyte apheresis uses a customized column through which only granulocytes and monocytes will pass. It takes the active granulocytes out of the bloodstream and usually takes three to four days. Blood is initially drawn from the right arm via the cubital vein, circulated via a customized column, and then returned to the leg. Even though the therapy requires ten sessions in total, the flow rate is 30 ml/min for two hours, twice a week. This new therapy is being utilized for both PG and IBD.[90,91]

Bioengineered skin and immunosuppression therapy

A spontaneous reduction in ulcer was seen after the graft skin insertion operation and cyclosporine medication. After 6 weeks of therapy, the PG lesion completely disappeared. The author draws a good conclusion about the combination of cyclosporine medication and allogeneic human skin equivalent. They explained how applying graft skin expedites wound healing, lessens discomfort, and lowers the possibility of side effects from long-term immunosuppressive drug treatment. Finally, it lessens contracture formation and enhances the cosmetic appearance of the lesion.[92].

Apligraft and immunosuppressive agent

Apligraft is a two-layered biological skin substitute made by Apligraft Organogenesis Inc. in Canton, Massachusetts. It is constructed of structural proteins and living cells. In numerous therapeutic situations, the use of Apligraft gave a favourable outcome in resistant ulcers.[93]

Surgical intervention and hyperbaric oxygen therapy

Surgery and hyperbaric oxygen therapy showed a favourable response in a patient with a rapidly sprouting ulcer and colorectal cancer. The patient did not respond well to the standard treatment modalities. Following immunosuppressive therapy, surgery, and hyperbaric oxygen therapy, this patient's lesion significantly improved clinically. Neither a recurrence nor any negative effect was noticed throughout treatment.[94]

Tripterygium wilfordii multiglycoside

It is an extract made in China from an herbal medicine with potent anti-inflammatory and immunosuppressive effects. Li and his team administered Tripterygium wilfordii orally in two cases of resistant PG. Over two weeks, there was a noticeable improvement, and after one month, there was a full resolution. However, gastrointestinal side effects and momentary changes in liver tests such as blood alanine transaminase (ALT) was observed. According to the author, the extract can be used as an efficient alternative therapy in resistant PG. however, careful monitoring of liver function enzymes is needed.[95]

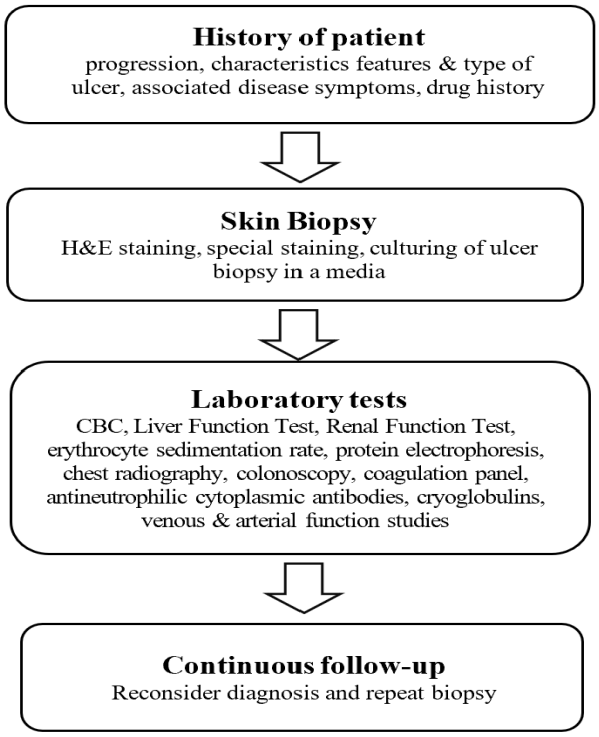

Figure-1: Schematic steps to be followed in the management of PG ulcers

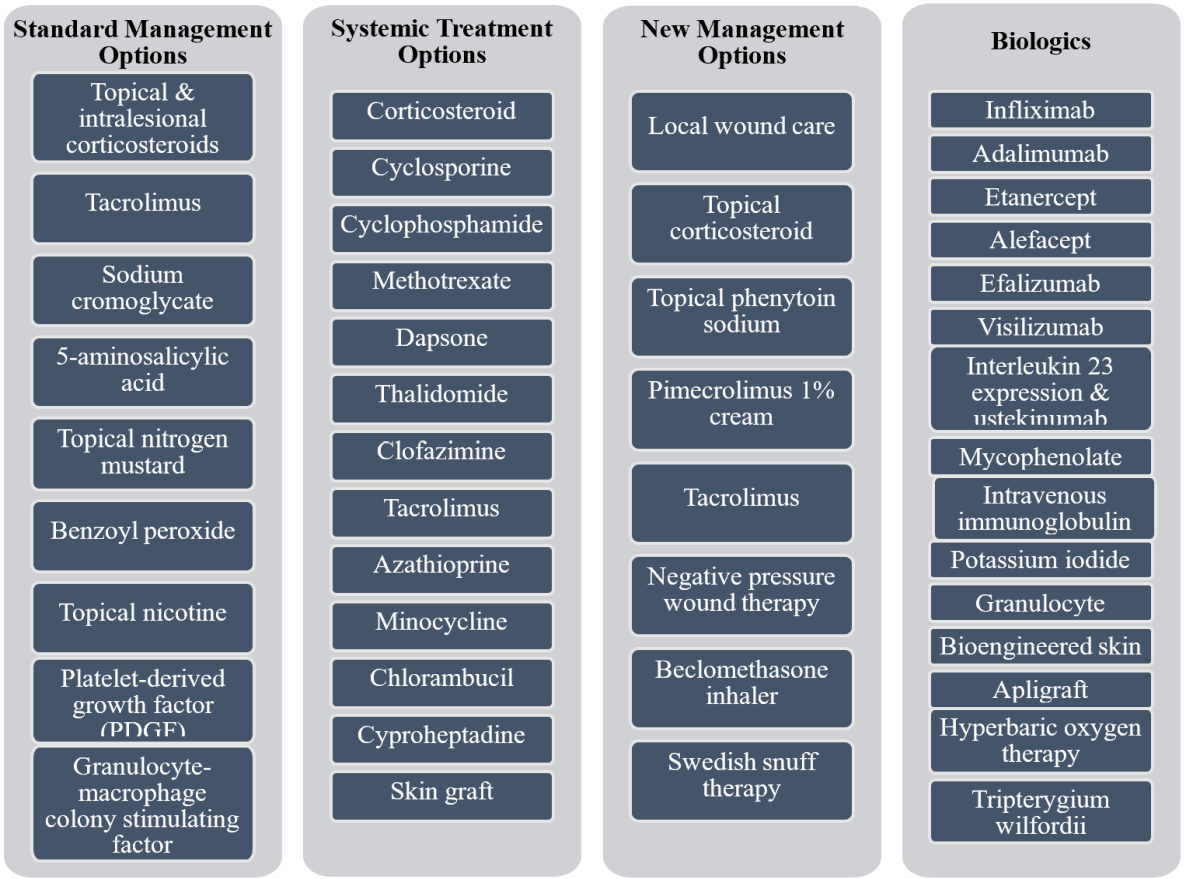

Figure-2: A summary of the standard, systemic and new treatment options for the management of PG.

DISCUSSION

Existing Gaps and Future Prospects

Despite several options for treatment, there is still a lack of a widely recognized therapeutic regimen to manage and treat PG because it is challenging to compare the efficacy of various treatment regimens due to variability in PG assessment and outcomes. The treatment of PG cases must include medical therapy as well as wound care with the right dressings based on the inflammatory vs. non-inflammatory phase. There are several issues related to PG management. Particularly in refractory cases that are associated with remission, the majority of the agents fail to achieve clinical improvement. The difference between idiopathic PG and PG with underlying associations is not particularly noticeable. Although it is acknowledged that systemic PG is more likely to return.[1,82]

Nevertheless, due to unknown aetiology and a dearth of carefully planned clinical studies, the therapeutic strategy is determined by the doctor's clinical opinion in each unique case rather than by an evidence-based decision. Due to a lack of sizable controlled studies, the optimal dosage and duration of therapies remain variable. Therefore, to gather sufficient data for the primary pathogenesis, aetiology, and management, a multidisciplinary strategy to research is imperative. In this view, future research is necessary to clarify the short- and long-term efficacy of old and novel treatments for PG. Large scale retrospective systematic cohort studies would be required to chart out the disease aetiologies, and prospective studies would be required to evaluate the efficacy of different treatment options to manage PG.

CONCLUSION

Recently, novel therapies for refractory PG were noted. Even though case reports and retrospective research make up the majority of the evidence for these more recent medicines, these drugs' mechanisms of action, long-term benefits, safety, and efficacy have not yet been determined. Even though these more recent therapies for recalcitrant PG seem promising and present the possibility for other treatments that function similarly, they must first be proven effective in prospective, double-blind, randomized controlled studies with long-term follow-up.

REFERENCES

1. George C, Deroide F, Rustin M. Pyoderma gangrenosum - a guide to diagnosis and management. Clin Med (Lond) 2019;19(3):224–8.
2. Wollina U. Pyoderma gangrenosum--a review. Orphanet J Rare Dis 2007;2:19.
3. Butcher M. Pyoderma gangrenosum: a diagnosis not to be missed. WOUNDS UK 2005;1(3):84.
4. Fulbright RK, Wolf JE, Tschen JA. Residents' corner: pyoderma gangrenosum at surgery sites. J Dermatol Surg Oncol 1985;11(9):883–6.
5. Adachi Y, Kindzelskii AL, Cookingham G, Shaya S, Moore EC, Todd RF 3rd, *et al*. Aberrant neutrophil trafficking and metabolic oscillations in severe pyoderma gangrenosum. J Invest Dermatol 1998;111(2):259–68.
6. van de Vijver E, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. Hematol Oncol Clin North Am 2013;27(1):101–16.
7. Su WP, Davis MD, Weenig RH, Powell FC, Perry HO. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol 2004;43(11):790–800.
8. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, *et al*. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58(5):826–50.
9. Sandborn WJ, Targan SR. Biologic therapy of inflammatory bowel disease. Gastroenterology 2002;122(6):1592–1608.
10. Chow RK, Ho VC. Treatment of pyoderma gangrenosum. J Am Acad Dermatol 1996;34(6):1047–60.
11. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg 2013;206(3):410–7.
12. Hughes AP, Jackson JM, Callen JP. Clinical features and treatment of peristomal pyoderma gangrenosum. JAMA 2000;284(12):1546–8.
13. Goldstein F, Krain R, Thornton JJ. Intralesional steroid therapy of pyoderma gangrenosum. J Clin Gastroenterol 1985;7(6):499–501.
14. Jennings J. Pyoderma gangrenosum: successful treatment with intralesional steroids. J Am Acad Dermatol 1983;9(4):575–80.
15. Homey B, Assmann T, Vohr HW, Ulrich P, Lauerma AI, Ruzicka T, *et al*. Topical FK506 suppresses cytokine and costimulatory molecule expression in epidermal and local draining lymph node cells during primary skin immune responses. J Immunol 1998;160(11):5331–40.
16. Schuppe HC, Homey B, Assmann T, Martens R, Ruzicka T. Topical tacrolimus for pyoderma gangrenosum. Lancet 1998;351(9105):832.
17. Reich K, Vente C, Neumann C. Topical tacrolimus for pyoderma gangrenosum. Br J Dermatol 1998;139(4):755–7.
18. Sehgal VN, Srivastava G, Dogra S. Tacrolimus in dermatology—pharmacokinetics, mechanism of action, drug interactions, dosages, and side effects: part I. Skinmed 2008;7(1):27–30.
19. Tamir A, Landau M, Brenner S. Topical treatment with 1% sodium cromoglycate in pyoderma gangrenosum. Dermatology 1996;192(3):252–4.
20. Saffouri B, Hom BM, Mertesdorf JM, Gardiner JF. Treatment of pyoderma gangrenosum with disodium cromoglycate. Dig Dis Sci 1984;29:183–5.
21. De Cock K, Thorne M. The treatment of pyoderma gangrenosum with sodium cromoglycate. Br J Dermatol 1980;102(2):231–3.
22. Sanders C, Hulsmans R. Successful treatment of pyoderma gangrenosum with topical 5-aminosalicylic acid. Cutis 1993;51(4):262–4.
23. Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. Am J Clin Dermatol 2012;13:191–211.
24. Tsele E, Yu R, Chu A. Pyoderma gangrenosum—response to topical nitrogen mustard. Clin Exp Dermatol 1992;17(6):437–40.
25. Nguyen L, Weiner J. Treatment of pyoderma gangrenosum with benzoyl peroxide. Cutis 1977;19(6):842–4.

26. Vereecken P, Wautrecht JC, De Dobbeleer G, Heenen M. A case of pyoderma gangrenosum stabilized with lymecycline, topical benzoyl peroxide and treated by autograft. Dermatology 1997;195(1):50–1.
27. Misery L. Nicotine effects on skin: are they positive or negative? Exp Dermatol 2004;13(11):665–70.
28. Wolf R, Ruocco V. Nicotine for pyoderma gangrenosum. Arch Dermatol 1998;134(9):1071–2.
29. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev 1999;79(4):1283–316.
30. Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)–a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol 2012;66(3):409–15.
31. Morrissey PJ, Grabstein KH, Reed SG, Conlon PJ. Granulocyte/macrophage colony stimulating factor. A potent activation signal for mature macrophages and monocytes. Int Arch Allergy Immunol 1989;88(1-2):40–5.
32. White LE, Villa MT, Petronic-Rosic V, Jiang J, Medenica MM. Pyoderma gangrenosum related to a new granulocyte colony-stimulating factor. Skinmed 2006;5(2):96–8.
33. Callen JP. Pyoderma gangrenosum. Lancet 1998;351(9102):581–5.
34. Lebbe C, Moulonguet-Michau I, Perrin P, Blanc F, Frja J, Civatte J. Steroid-responsive pyoderma gangrenosum with vulvar and pulmonary involvement. J Am Acad Dermatol 1992;27(4):623–5.
35. Gupta AK, Brown MD, Ellis CN, Rocher LL, Fisher GJ, Baadsgaard O, *et al*. Cyclosporine in dermatology. J Am Acad Dermatol 1989;21(6):1245–56.
36. Matis WL, Ellis CN, Griffiths CE, Lazarus GS. Treatment of pyoderma gangrenosum with cyclosporine. Arch Dermatol 1992;128(8):1060–4.
37. Gasior-Chrzan B, Stenvold S, Falk E. Treatment of pyoderma gangrenosum with cyclosporine. J Eur Acad Dermatol Venereol 1995;5:S162.
38. Ahmed AR, Hombal SM. Cyclophosphamide (Cytoxan): a review on relevant pharmacology and clinical uses. J Am Acad Dermatol 1984;11(6):1115–26.
39. Newell LM, Malkinson FD. Pyoderma gangrenosum: response to cyclophosphamide therapy. Arch Dermatol 1983;119(6):495–7.
40. Crawford SE, Sherman R, Favara B. Pyoderma gangrenosum with response to cyclophosphamide therapy. J Pediatr 1967;71(2):255–8.
41. Cronstein BN. Molecular therapeutics. Methotrexate and its mechanism of action. Arthritis Rheum 1996;39(12):1951–60.
42. Teitel A. Treatment of pyoderma gangrenosum with methotrexate. Cutis 1996;57(5):326–8.
43. Brown R, Lay L, Graham D. Bilateral pyoderma gangrenosum of the hand: treatment with dapsone. J Hand Surg 1993;18(1):119–21.
44. Perri III AJ, Hsu S. A review of thalidomide's history and current dermatological applications. Dermatol Online J 2003;9(3):5.
45. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. Mayo Clin Proc 2000;75(8):842–4.
46. Thomsen K, Rothenborg HW. Clofazimine in the treatment of pyoderma gangrenosum. Arch Dermatol 1979;115(7):851–2.
47. Michaëlsson G, Molin L, Ohmann S, Gip L, Lindström B, Skogh M, *et al*. Clofazimine: a new agent for the treatment of pyoderma gangrenosum. Arch Dermatol 1976;112(3):344–9.
48. Abu-Elmagd K, Van Thiel DH, Jegasothy BV, Jacobs JC, Carroll P, Rodriquez-Rilo H, *et al*. Resolution of severe pyoderma gangrenosum in a patient with streaking leukocyte factor disease after treatment with tacrolimus (FK 506). Ann Intern Med 1993;119(7_Part_1):595–8.
49. Weichert G, Sauder DN. Efficacy of tacrolimus (FK 506) in idiopathic treatment-resistant pyoderma gangrenosum. J Am Acad Dermatol 1998;39(4):648–50.
50. Bhat RM. Management of pyoderma gangrenosum–An update. Indian J Dermatol Venereol Leprol 2004;70(6):329–35.
51. Breathnach S, Wells G, Valdimarsson H. Idiopathic pyoderma gangrenosum and impaired lymphocyte function: failure of azathioprine and corticosteroid therapy. Br J Dermatol 1981;104(5):567.
52. Davies M, Piper S. Pyoderma gangrenosum: successful treatment with minocycline. Clin Exp Dermatol 1981;6(2):219–23.
53. Burruss JB, Farmer ER, Callen JP. Chlorambucil is an effective corticosteroid-sparing agent for recalcitrant pyoderma gangrenosum. J Am Acad Dermatol 1996;35(5):720–4.
54. Gelernt I, Kreel I. Pyoderma gangrenosum in ulcerative colitis: prevention of the gangrenous component. Mt Sinai J Med 1976;43(4):467–70.
55. Cliff S, Holden CA, Thomas PR, Marsden RA, Harland CC. Split skin grafts in the treatment of pyoderma gangrenosum: a report of four cases. Dermatol Surg 1999;25(4):299–302.
56. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: A practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol 2008;58(2):185–206.
57. Gottrup F, Karlsmark T. Leg ulcers: uncommon presentations. Clin Dermatol 2005;23(6):601–11.
58. Le Cleach L, Moguelet P, Perrin P, Chosidow O. Is topical monotherapy effective for localized pyoderma gangrenosum? Arch Dermatol 2011;147(1):101–3.
59. Fonseka HF, Ekanayake SM, Dissanayake M. Two percent topical phenytoin sodium solution in treating pyoderma gangrenosum: a cohort study. Int Wound J 2010;7(6):519–23.
60. Bellini V, Simonetti S, Lisi P. Successful treatment of severe pyoderma gangrenosum with pimecrolimus cream 1%. J Eur Acad Dermatol Venereol 2008;22(1):113–5.
61. Piccirillo A, Ricciuti F. Topical tacrolimus for pyoderma gangrenosum: another report. J Dermatol 2006;33(3):232.
62. Chiba T, Kiehl P, Breuer C, Kapp A, Werfel T. Topical tacrolimus therapy for pyoderma gangrenosum. J Dermatol 2005;32(3):199–203.
63. Fraccalvieri M, Fierro MT, Salomone M, Fava P, Zingarelli EM, Cavaliere G, *et al*. Gauze-based negative pressure wound therapy: a valid method to manage pyoderma gangrenosum. Int Wound J 2014;11(2):164–8.
64. Chriba M, Skellett A, Levell N. Beclometasone inhaler used to treat pyoderma gangrenosum. Clin Exp Dermatol 2010;35(3):337–8.
65. Kluger N. Can snus (Swedish moist snuff) be used as a treatment of Pyoderma gangrenosum? Med Hypotheses 2012;78(5):619–20.
66. Rutgeerts P, Vermeire S, Van Assche G. Biological therapies for inflammatory bowel diseases. Gastroenterology 2009;136(4):1182–97.
67. Reguiai Z, Grange F. The role of anti-tumor necrosis factor-α therapy in pyoderma gangrenosum associated with inflammatory bowel disease. Am J Clin Dermatol 2007;8:67–77.
68. Gisondi P, Girolomoni G. Biologic therapies in psoriasis: a new therapeutic approach. Autoimmun Rev 2007;6(8):515–9.
69. Brooklyn TN, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, *et al*. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut 2006;55(4):505–9.
70. Regueiro M, Valentine J, Plevy S, Fleisher MR, Lichtenstein GR. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. Am J Gastroenterol 2003;98(8):1821–6.

71. Traczewski P, Rudnicka L. Adalimumab in dermatology. Br J Clin Pharmacol 2008;66(5):618–25.
72. Fonder MA, Cummins DL, Ehst BD, Anhalt GJ, Meyerle JH. Adalimumab therapy for recalcitrant pyoderma gangrenosum. J Burns Wounds 2006;5:e8.
73. Heffernan MP, Anadkat MJ, Smith DI. Adalimumab treatment for pyoderma gangrenosum. Arch Dermatol 2007;143(3):306–8.
74. Goffe B, Cather JC. Etanercept: an overview. J Am Acad Dermatol 2003;49(2):105–11.
75. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, *et al*. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003;3(3):148–55.
76. Pastor N, Betlloch I, Pascual JC, Blanes M, Bañuls J, Silvestre JF. Pyoderma gangrenosum treated with anti-TNF alpha therapy (etanercept). Clin Exp Dermatol 2006;31(1):152–3.
77. Goldenberg G, Jorizzo JL. Use of etanercept in treatment of pyoderma gangrenosum in a patient with autoimmune hepatitis. J Dermatol Treat 2005;16(5-6):347–9.
78. Charles CA, Leon A, Banta MR, Kirsner RS. Etanercept for the treatment of refractory pyoderma gangrenosum: a brief series. Int J Dermatol 2007;46(10):1095–9.
79. Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G. Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol 2009;23(9):1008–17.
80. Graves JE, Nunley K, Heffernan MP. Off-label uses of biologics in dermatology: rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept (part 2 of 2). J Am Acad Dermatol 2007;56(1):e55–79.
81. Foss CE, Clark AR, Inabinet R, Camacho F, Jorizzo JL. An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. J Eur Acad Dermatol Venereol 2008;22(8):943–9.
82. Miller J, Yentzer BA, Clark A, Jorizzo JL, Feldman SR. Pyoderma gangrenosum: a review and update on new therapies. J Am Acad Dermatol 2010;62(4):646–54.
83. Wollina U, Haroske G. Pyoderma gangraenosum. Curr Opin Rheumatol 2011;23(1):50–6.
84. Lorincz M, Kleszky M, Szalóki T Jr, Szalóki T. Pyoderma gangrenosum treated successfully with visilizumab in patients with ulcerative colitis. Orv Hetil 2010;151(4):144–7.
85. Guenova E, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, *et al*. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. Arch Dermatol 2011;147(10):1203–5.
86. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000;47(2-3):85–118.
87. Eaton PA, Callen JP. Mycophenolate mofetil as therapy for pyoderma gangrenosum. Arch Dermatol 2009;145(7):781–5.
88. Cummins DL, Anhalt GJ, Monahan T, Meyerle JH. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. Br J Dermatol 2007;157(6):1235–9.
89. Qiu L, Zheng S, Wu J, Xiao T, Chen HD. Refractory disseminated pyoderma gangrenosum, with dependence on corticosteroids, responding to potassium iodide. Eur J Dermatol 2012;22(3):426–7.
90. Saniabadi AR, Hanai H, Takeuchi K, Umemura K, Nakashima M, Adachi T, *et al*. Adacolumn, an Adsorptive Carrier Based Granulocyte and Monocyte Apheresis Device for the Treatment of Inflammatory and RefractoryDiseases Associated with Leukocytes. Ther Apher Dial 2003;7(1):48–59.
91. Okuma K, Mitsuishi K, Hasegawa T, Tsuchihashi H, Ogawa H, Ikeda S. A case report of steroid and immunosuppressant-resistant pyoderma gangrenosum successfully treated by granulocytapheresis. Ther Apher Dial 2007;11(5):387–90.
92. de Imus G, Golomb C, Wilkel C, Tsoukas M, Nowak M, Falanga V. Accelerated healing of pyoderma gangrenosum treated with bioengineered skin and concomitant immunosuppression. J Am Acad Dermatol 2001;44(1):61–6.
93. Duchini G, Itin P, Arnold A. A case of refractory pyoderma gangrenosum treated with a combination of Apligraf and systemic immunosuppressive agents. Adv Skin Wound Care 2011;24(5):217–20.
94. Altunay I, Kucukunal A, Sarikaya S, Tukenmez Demirci G. A favourable response to surgical intervention and hyperbaric oxygen therapy in pyoderma gangrenosum. Int Wound J 2014;11(4):350–3.
95. Li LF. Treatment of pyoderma gangrenosum with oral Tripterygium wilfordii multiglycoside. J Dermatol 2000;27(7):478–81.

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